Monatshefte für Chemie - Chemical Monthly (2020) 151:781–789
https://doi.org/10.1007/s00706-020-02601-w

ORIGINAL PAPER

One pot, multicomponent protocol for the synthesis of novel imidazo[1,2-*a*]pyrimidine-based pyran analogs: a potential biological scaffold

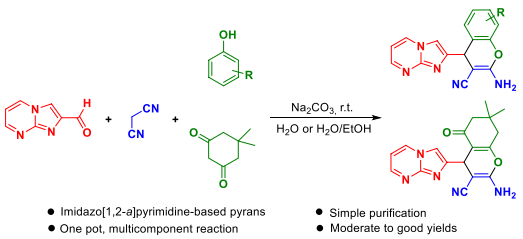
Tuğba Güngör[1]

Received: 11 February 2020 / Accepted: 4 April 2020 / Published online: 12 May 2020

Abstract

An efficient procedure between imidazo[1,2-*a*]pyrimidine-2-carbaldehyde, malononitrile, enolizable C–H activated acidic compounds, and sodium carbonate is described for the synthesis of potential biologically active, novel imidazo[1,2-*a*]-pyrimidine-based pyran analogs through one pot, multicomponent reactions at room temperature. This method provided mild reaction conditions, simple purification without column chromatography, and moderate to good yields for the construction of imidazo[1,2-*a*]pyrimidine-based pyran derivatives. The structures of target compounds were established with different spectroscopic analyses.

Graphic abstract



Keywords Chromenes · Imidazo[1,2-*a*]pyrimidines · Pyrans · Multicomponent reactions (MCRs) · One-pot synthesis

Introduction

Due to the increasing concern about various diseases, more attention of multidisciplinary scientists has focused on the development of new, more effective treatments and novel drug molecules. Hence, heterocyclic compounds have recently attracted much more interest because of their useful pharmacological and biological properties. One of these is pyrans which are found in natural sources. An important member of pyrans is 4*H*-chromenes which are bicyclic oxygen heterocycles formed as a result of the fusion of benzene ring with 5,6-positions of 4*H*-pyran ring. 4*H*-Chromenes have been evaluated to exhibit significant pharmacological potential in a broad range of applications in relation to anticancer [1], antiinflammatory [2], acetylcholinesterase (AChE) inhibitory [3], anti-rheumatic [4], neurodegenerative diseases (Alzheimer, Down syndrome, Schizophrenia and Huntington) [5, 6], antimicrobial [7], antibacterial [8–10], antifungal properties [8, 11], and so on. They are also useful in fluorescence, pigment, optical, cosmetic, and agricultural applications [12]. Several methods have been reported for development of different catalysts under various conditions for one-pot, multicomponent synthesis of numerous

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00706-020-02601-w) contains supplementary material, which is available to authorized users.

✉ Tuğba Güngör
tgungor@comu.edu.tr

[1] Department of Chemistry, Faculty of Sciences and Arts, Natural Products and Drug Research Laboratory, Çanakkale Onsekiz Mart University, Çanakkale, Turkey

2-amino-3-cyano-4*H*-pyran derivatives due to their versatility and superior biological properties [5, 13–18].

Another important class of these heterocyclic compounds is imidazo[1,2-*a*]pyrimidines which are formed as a result of the fusion of imidazole and pyrimidine moieties. Imidazo[1,2-*a*]pyrimidines were evaluated to exhibit significant therapeutic potential linked to anticancer [19–21], cardiovascular [22], antibacterial [23], antimicrobial [21, 24], antifungal [25], antiviral [26], anti-inflammatory [27], HIV inhibitor [28], local anesthetic [29], P38 MAP kinase inhibitor properties [30] and in some agrochemicals [21, 31–34]. Many commercially available drugs, such as fasiplon, taniplon, and divaplon which are anxiolytic and anticonvulsant agents contain imidazo[1,2-*a*]pyrimidine moiety [35–37] (Fig. 1).

Multicomponent reactions (MCRs) are the beneficial and practical tools to synthesize complex functional heterocyclic scaffolds which combine three or more readily available starting materials through an one-pot approach. These types of reactions provide a lot of advantages such as rapid and selective product formation, high atom economy, low cost, minimum waste, and environmental friendliness compared with conventional multi-step reactions [38, 39].

Considering the remarkable medicinal applications of imidazo[1,2-*a*]pyrimidines and pyrans, the combination of these two scaffolds in a single molecule could be an important starting point for drug research. Some examples of the most active imidazo[1,2-*a*]pyrimidine and pyran compounds are presented in Fig. 1.

Herein, a simple and efficient procedure is reported for the synthesis of imidazo[1,2-*a*]pyrimidine-based pyran derivatives via one-pot three component reaction of imidazo[1,2-*a*]-pyrimidine-2-carbaldehyde, malononitrile, and enolizable C–H activated acidic compounds in the presence of sodium carbonate in water or a mixture of ethyl alcohol/water as solvent at room temperature conditions (Scheme 1). All the products were fully characterized with various spectral analyses including FT-IR, ^{1}H NMR, ^{13}C NMR, and MS. It is expected that the studied molecules including two different pharmacophores show good prospective biological and pharmacological activities.

Results and discussion

Initially, imidazo[1,2-*a*]pyrimidine-2-carbaldehyde as starting material was obtained in a two-step synthetic procedure using the Chichibabin method as described in the literature [40] and the structure of the compound was compared with reported spectral data [40, 41]. While the first step is a condensation reaction with 2-aminopyrimidine and 1,1,3-trichloroacetone in THF, the second step consists of a hydrolysis reaction of the HCl salt of the fused biheterocycle with sodium acetate in water.

Then, the main investigation was initiated with a one-pot, multicomponent reaction of imidazo[1,2-*a*]pyrimidine-2-carbaldehyde (**1**), malononitrile (**2**), and resorcinol (**3a**) which was selected as a model reaction to synthesize compound **4a** (Table 1). First, the conditions consisted of sodium carbonate (0.45 eq.) in H_2O/EtOH as a solvent mixture at 25 °C ambient temperature for 24 h which resulted in 53% yield of product **4a** according to the modified method in Ref. [8] (Table 1, entry 1). When using distilled water alone as solvent with the same amount of Na_2CO_3, the reaction

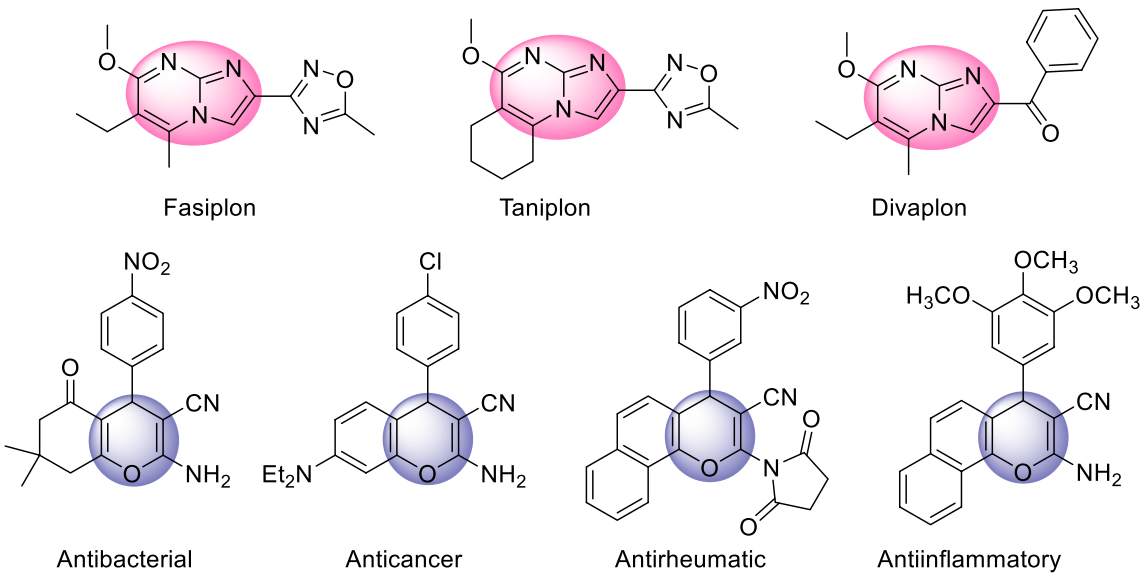
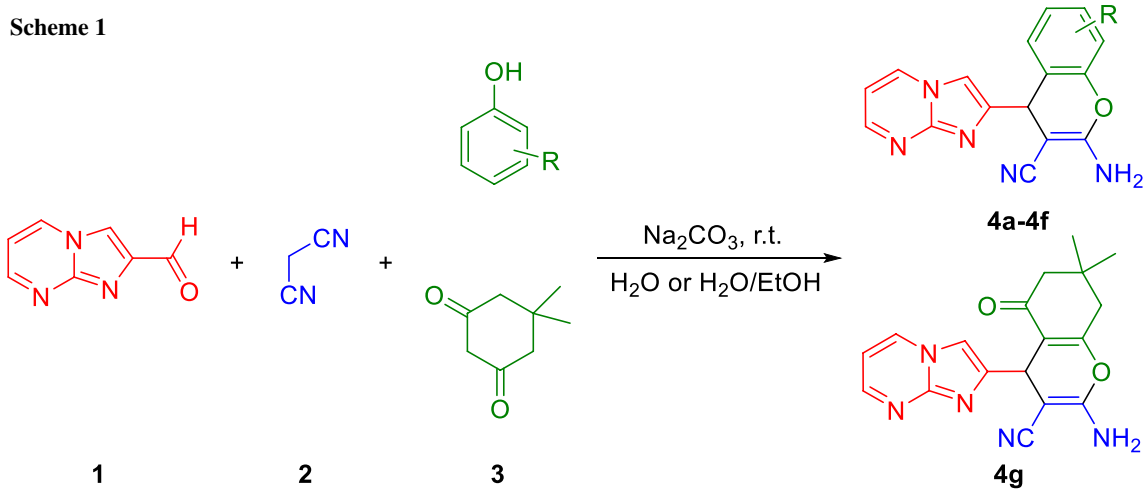


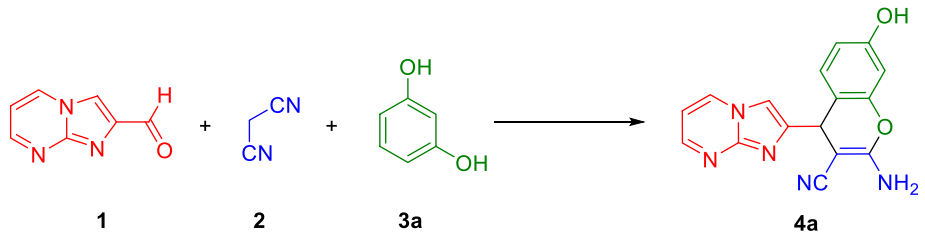
Fig. 1 Structures of pharmacologically useful imidazo[1,2-*a*]pyrimidines and 4*H*-pyrans

Scheme 1



completed in 16 h at room temperature with same moderate yield, 53% due to the limited base (Table 1, entry 3). It was observed that the product yield was decreased to 39% with 75 °C heating of the EtOH/H_2O solvent mixture with the same amount of Na_2CO_3 (Table 1, entry 2). While the reflux conditions of 0.45 equiv. Na_2CO_3 in water resulted in 3 h reaction time and 60% yield, the reflux conditions of 1.3 equiv. Na_2CO_3 in water gave 1 h reaction time and 24% yield (Table 1, entries 4 and 6). Increasing the quantity of sodium carbonate to 1.3 equiv. resulted in a significantly higher yield (83%) and shorter reaction time (2 h) (Table 1, entry 5). Furthermore, a nitrogen containing organic base, piperazine (30% mol), was used instead of sodium carbonate to investigate the effect of base type (Table 1, entries 7, 8). The room temperature reaction was completed in a long time (48 h) and led to moderate yield of **4a**, 51% (Table 1, entry

Table 1 Optimization of the reaction conditions for the synthesis of 2-amino-7-hydroxy-4-(imidazo[1,2-*a*]pyrimidin-2-yl)-4*H*-chromene-3-carbonitrile (**4a**)



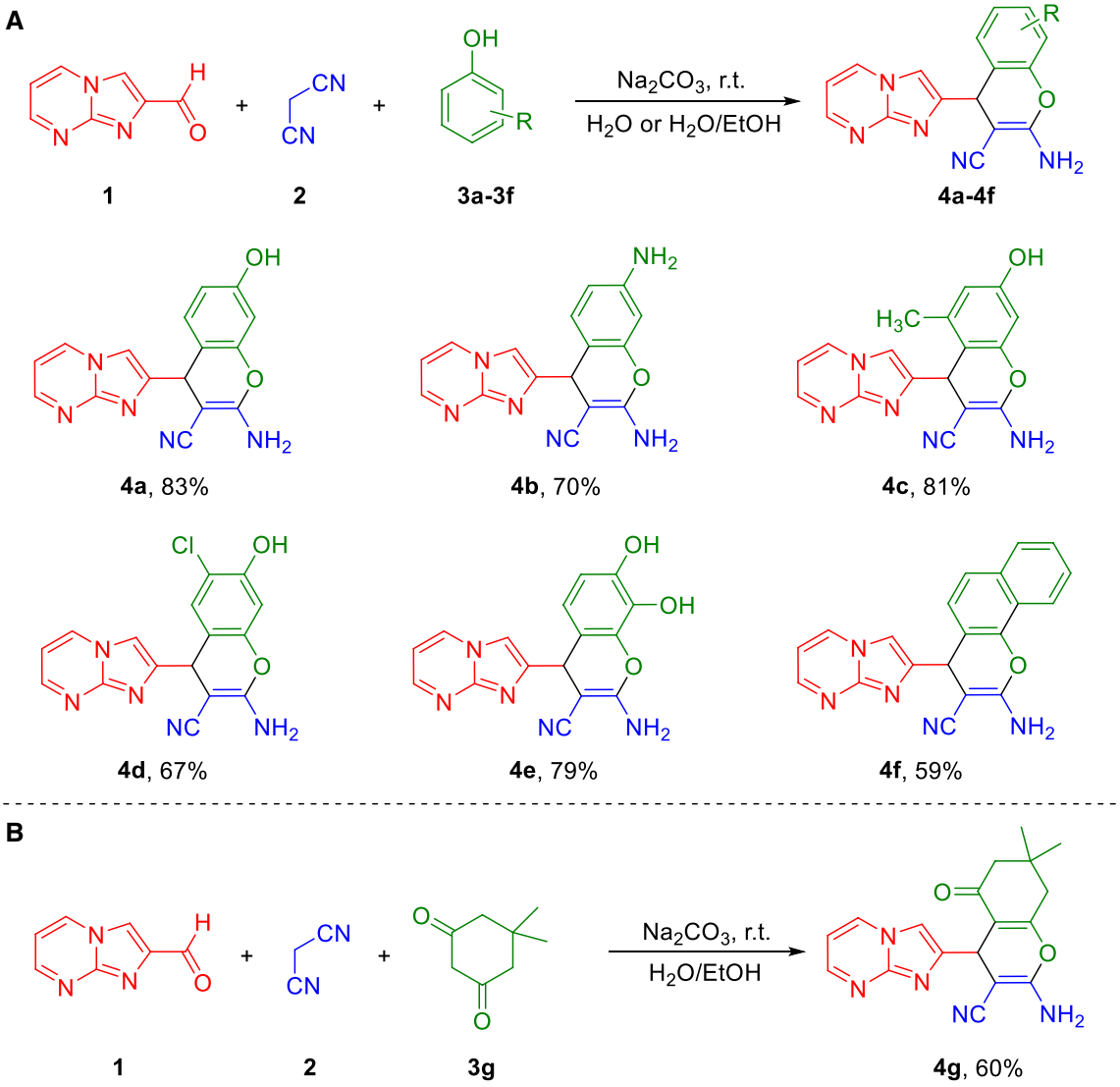
Entry	Base	Solvent	Temperature	Time/h	Yield[a]/%
1	Na_2CO_3 (0.45 equiv.)	EtOH/H_2O	rt	24	53
2	Na_2CO_3 (0.45 equiv.)	EtOH/H_2O	75 °C	2.5	39
3	Na_2CO_3 (0.45 equiv.)	H_2O	rt	16	53
4	Na_2CO_3 (0.45 equiv.)	H_2O	Reflux	3	60
5	**Na_2CO_3 (1.3 equiv.)**	**H_2O**	**rt**	**2**	**83**
6	Na_2CO_3 (1.3 equiv.)	H_2O	Reflux	1	24
7	Piperazine (30% mol)	H_2O	rt	48	51
8	Piperazine (30% mol)	H_2O	Reflux	3	40
9	Na_2CO_3 (1.3 equiv.)	H_2O	MW-30 °C	0.2	56
10	Na_2CO_3 (1.3 equiv.)	H_2O	MW-70 °C	0.33	61

[a]Yield of isolated product

7). Increasing the reaction temperature led to a shortening of time to 3 h and also decreased the product yield, 40% (Table 1, entry 8). Microwave irradiation (50 W and 30 °C) was applied to the reaction mixture of model compound **4a** and product was obtained in 12 min with 56% yield (Table 1, entry 9). When microwave energy (200 W) was irradiated at 70 °C, it was observed that the reaction completed in 20 min but the yield decreased to 61% compared to the best result (Table 1, entry 10). Consequently, increasing the temperature of the EtOH/H_2O mixture or only H_2O in the presence of sodium carbonate or piperazine resulted lower yields of **4a** due to the formation of new by-products (Table 1, entries 2, 6, 8, and 10). When all outputs are evaluated, the best result was obtained using 1.0 equiv. imidazo[1,2-*a*]pyrimidine-2-carbaldehyde, 1.3 equiv. malononitrile, 1.3 equiv. resorcinol, and 1.3 equiv. sodium carbonate in H_2O at room temperature. The optimization results of **4a** are shown in Table 1.

After reaching optimum conditions, various phenol derivatives (resorcinol, 3-aminophenol, orcinol, 4-chlororesorcinol, pyrogallol, and 1-naphthol) were utilized in the optimized one-pot multicomponent reaction conditions and the corresponding products **4a**–**4f** were successfully obtained in short reaction times (2–7 h) and moderate to high yields (59–83%) at room temperature (Scheme 2). Furthermore, dimedon as an enolizable C–H activated acidic compound was also used as substrate in the optimized conditions and the desired product **4g** was synthesized with 60% yield. It was observed that compounds **4b** and **4f** have longer reaction times (5 and 7 h, respectively) than other compounds (2–3 h)

Scheme 2



due to the partially lower reactivity of 3-aminophenol and 1-naphthol. In addition, when phenol or phenol derivatives containing electron-withdrawing functional groups such as 4-chlorophenol, 2-, 3-, 4-nitrophenols, or 4-nitrocatechol, were used as enolizable components, reactions occurred inefficiently with long reaction times and the desired pyran products were observed to have very low yields (< 10%). According to the TLC tracking, the first step occurs smoothly and the common condensation product forms successfully. However, one of the following steps fails due to the unstable intermediates caused by electron-withdrawing functional groups and the final pyran compounds could not be obtained efficiently. All the synthesized final products are novel and were fully characterized with their analytical data and spectral analyses including FT-IR, ^{1}H NMR, ^{13}C NMR, and MS (see "Experimental" section and Supplementary data).

Mechanistically, the final products are obtained in three main steps including Knoevenagel condensation, Michael addition, and heterocyclization reactions, respectively, similar to the data reported in the literature [5, 16, 17]. Based on this approach, the reaction starts with the formation of carbanion intermediate **I** from malononitrile-active methylene compound and the attack of this intermediate to the carbonyl of imidazo[1,2-*a*]pyrimidine-2-carbaldehyde to form the olefin intermediate **II** as Knoevenagel product. In the second step, Michael type addition occurs between intermediate **II** and sodium phenolate derivatives which is formed by phenol derivatives and sodium carbonate to give intermediate **III** as addition product. Cyclization starts with deprotonation by base on intermediate **III** and following a series of intramolecular rearrangements result in formation of the aromatic intermediate **IV** which produced the desired heterocyclic products (imidazo[1,2-*a*]pyrimidine-based pyrans **4a**–**4g**) through imine-enamine tautomerization. The importance of sodium carbonate as base in the mechanism can be observed clearly at three points which are deprotonation of the active methylene compound at the beginning of the mechanism, formation the enolate intermediate of phenol derivatives and deprotonation of intermediate **III** to initiate cyclization. A plausible mechanism for the formation of imidazo[1,2-*a*]-pyrimidine-based 4*H*-pyrans is shown in Scheme 3.

The spectra and values of products **4a**–**4g** are given in the Experimental section and Supplementary data. In brief, all compounds exhibited N–H stretching and bending bands of -NH_2 group at 3448–3303 cm^{-1} and 1658–1645 cm^{-1} in FT-IR spectra. The other major feature of the compounds was strong cyano (–CN) band at 2197–2185 cm^{-1} in the triple bond stretch region. In addition, aromatic C–H stretching and bending bands were generally at 3190–3006 cm^{-1} and 1620–1611 cm^{-1} frequency range, respectively. In addition, C=N and C=C stretching bands of imidazo[1,2-*a*]pyrimidine were in a similar range, 1658–1645 cm^{-1}. While aliphatic C–H stretching absorption of the pyran ring was observed at

Scheme 3

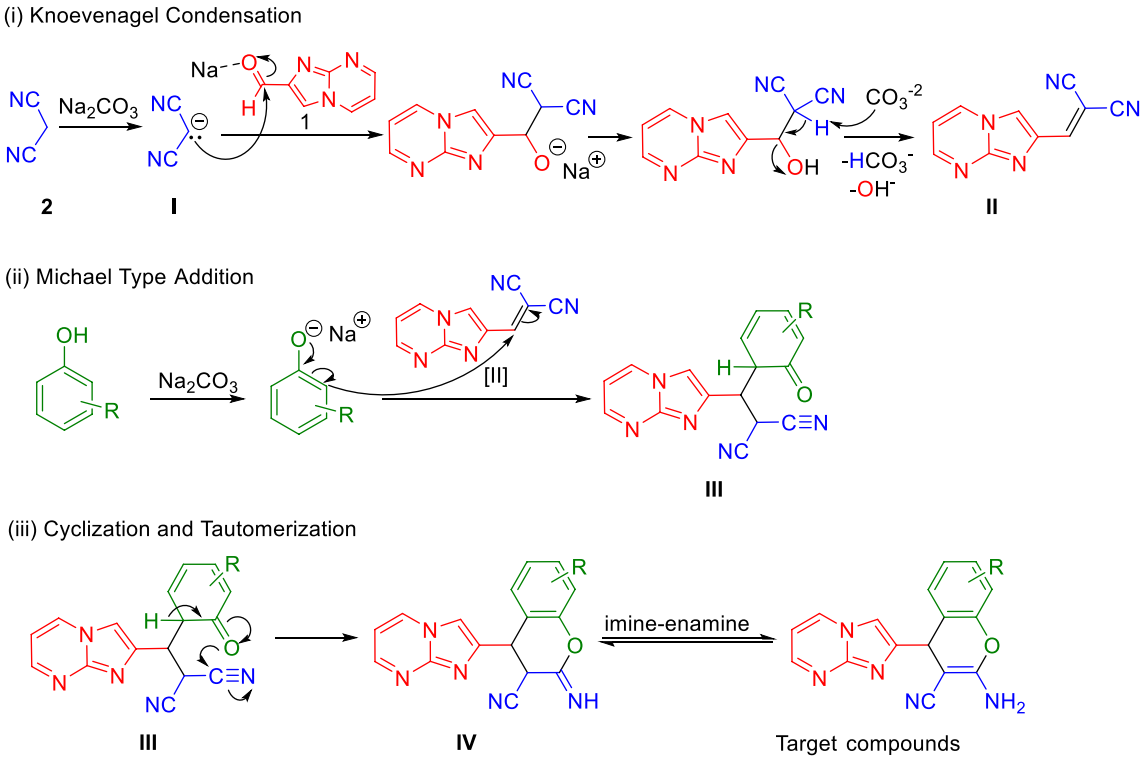
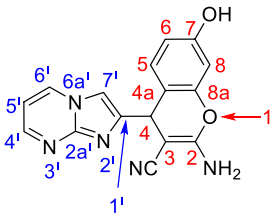


Table 2 ^{1}H NMR and ^{1}H-^{1}H COSY data for compound **4a**



Assign	Chemical shift/ppm	Multiplicity	Coupling constant/Hz	Integration	^{1}H–^{1}H COSY correlation/ppm
OH	9.86	s	–	1H	–
H-6^{1}	8.52	dd	3.90 and 1.89	1H	8.48 and 7.04
H-4^{1}	8.48	dd	6.88 and 1.61	1H	8.52 and 7.04
H-7^{1}	7.63	s	–	1H	–
NH_2	7.11	s	–	2H	–
H-5^{1}	7.04	dd	4.1 and 2.73	1H	8.52 and 8.48
H-5	6.73	t	4.55	1H	6.46
H-6, H-8	6.46	m	–	2H	6.73
H-4	5.41	s	–	1H	–

2990–2863 cm^{-1} as weak peak, C–O–C stretching band of pyran was determined at 1168–1139 cm^{-1} as strong peak. Other functional groups of varying compounds were monitored in expected regions of the IR spectra.

If the model compound **4a** is examined spectroscopically in detail, peaks were observed in the range of 9.86–5.41 ppm on ^{1}H NMR spectrum (Table 2). A total of four singlet peaks, three of them corresponding 1H integration and one peak corresponding 2H integration, were detected. The characteristic singlet peak with 2H integration at 7.10 ppm belongs to NH_2 group. The broad singlet signal which was in the low-field part of the ^{1}H NMR spectrum (9.86 ppm) confirms the presence of -OH group. The lowest singlet chemical shift (5.41 ppm) belongs to H-4 proton of the pyran ring. Therefore, the last singlet peak at 7.63 ppm corresponds to H-7^{1} proton of imidazole unit in the imidazo[1,2-*a*]pyrimidine ring. The other non-singlet aromatic peaks of pyrimidine and chromene rings were confirmed by two-dimensional NMR analysis. In the ^{13}C NMR spectrum, the signals of C-3 and C-4 of the pyran unit were located in the high-field part of the spectrum (52.30 and 30.56 ppm, respectively). The other 14 carbons were observed in the region of 161.41–103.04 ppm as expected (Table 3).

Table 3 ^{13}C NMR, HSQC, and HMBC data for compound **4a**

Assign	Chemical shift/ppm	HSQC correlation/ppm	HMBC correlation/ppm
C-2	161.41	–	7.11 and 5.41
C-7	158.20	–	9.86 and 6.73
C-6^{1}	150.00	8.52	8.48 and 7.04
C-8a	149.81	–	7.11, 6.73, 6.46, and 5.41
C-2a^{1}	148.58	–	7.63
C-7^{1}	134.00	7.63	5.39
C-4^{1}	132.59	8.48	8.52 and 7.04
C-5	129.27	6.73	5.41
C-1^{1}	125.14	–	7.63 and 5.41
CN	120.40	–	5.41
C-8	113.17	6.46	9.86 and 6.46
C-4a	109.90	–	6.46 and 5.41
C-5^{1}	109.23	7.04	8.52 and 8.48
C-6	103.04	6.46	9.86, 6.73, and 6.46
C-3	52.30	–	7.11 and 5.41
C-4	30.56	5.41	6.73

In addition, to determine the exact structure of compound **4a**, two-dimensional homonuclear (^{1}H-^{1}H COSY) and heteronuclear correlation analyses (^{1}H–^{13}C HSQC and HMBC) were performed. Signal assignments of ^{1}H, ^{13}C and two-dimensional NMR correlations for compound **4a** are presented in Tables 2 and 3. According to COSY spectrum, the three doublets of doublets peak at 7.04, 8.48, and 8.52 ppm in the low-field of spectrum are correlated with each other, which were assigned as H-5^{1}, H-4^{1}, and H-6^{1} of pyrimidine unit, respectively. HMBC results also confirmed this view about protons H-5^{1}, H-4^{1}, and H-6^{1}. In addition, chemical shifts at 6.73 ppm (1H) and 6.46 ppm (2H) had COSY correlation with each other, which were assigned as H-5, H-6, and H-8 of phenyl unit in the chromene ring, respectively. Protons

H-6 and H-8 attached to the -OH containing carbon atom overlapped with 2H integration as a multiplet peak. According to HSQC interactions, it was concluded that signals at 150.00, 134.00, 132.59, 129.27, 113.17, 109.23, 103.04, and 30.56 ppm corresponded to carbons C-6[1], C-7[1], C-4[1], C-5, C-8, C-5[1], C-6, C-4, respectively (Table 3). Chemical shifts of carbons C-6 and C-8 were determined as a result of the extra HMBC correlation of C-6 with proton H-5. In addition, carbon C-2 gave HMBC correlation with -NH_2 group and proton H-4 at the highest chemical shift, 161.41 ppm. The second highest value, 158.20 ppm, belongs to carbon C-7 due to the HMBC correlation with C-5 and -OH group. While carbon C-2a[1] at 148.58 ppm gave HMBC correlation with only proton H-7[1], the carbon of -CN group at 120.40 ppm correlates with only proton H-4. Ipso-carbon of imidazole ring (C-1[1]) correlates with protons H-7[1] and H-4 at 125.14 ppm. On the other hand, carbons C-4a and C-8a in the fused zone of the chromene unit were observed at 109.90 and 149.81 ppm due to the correlations with protons H-4, H6/H8 (for C-4a) and protons -NH_2, H-4, H-5 and H-8 (for C-8a).

According to the positive mode of the LC–MS spectrum for model compound **4a** contains the highest peak intensity (100%) of the molecular ion (*m/z* = 306, $C_{16}H_{11}N_5O_2$). The first fragmentation (*m/z* = 279) with 40% relative intensity is probably formed by the elimination of the cyano group. In addition, other final products were confirmed with the observation of their molecular ion peaks in the LC–MS spectra.

Conclusion

In summary, a simple and efficient one-pot, multicomponent synthesis method was developed for the potential biologically active novel imidazo[1,2-*a*]pyrimidine-based pyran derivatives **4a**–**4g** from imidazo[1,2-*a*]pyrimidine-2-carbaldehyde, malononitrile, and enolizable C–H activated acidic components in the presence of sodium carbonate using water or a mixture of ethyl alcohol/water as solvent under room temperature conditions. The applied method has some privileged advantages such as mild reaction conditions, simple work-up and purification techniques, and moderate to good product yields (59–83%). The structures of all newly-synthesized compounds were elucidated by melting point, FT-IR, ^{1}H NMR, ^{13}C NMR, and MS spectra. The biological studies of novel imidazo[1,2-*a*]pyrimidine-based pyran analogs **4a**–**4g** are ongoing in our research group.

Experimental

Commercially available reagents and solvents (Sigma-Aldrich, Merck, ABCR, Alfa Aesar, TCI, VWR, and Acros) were used without further purification. Melting points were determined by X-4 melting point apparatus. Thin layer chromatography was carried out using aluminum plates coated with Kieselgel silica gel 60GF_{254}. Analyses were performed by visualizing under UV light (λ = 254 and 366 nm) and $KMnO_4$ stain. IR spectra were recorded using Perkin Elmer Spectrum 100 FTIR spectrophotometer. ^{1}H and ^{13}C spectra were recorded using Jeol 400 MHz NMR spectrometer with DMSO-d_6 as the analysis solvent. ^{1}H, ^{13}C, COSY, HMBC, and HSQC analyses of compound **4a** were obtained using Agilent 600 MHz High-Performance Digital FT-NMR spectrometer. The chemical shifts are presented in ppm using TMS as an internal reference. Multiplicity (s: singlet, d: doublet, dd: doublet of doublet, t: triplet, q: quartet, m: multiplet) and coupling constants (*J*: Hz) are quoted where possible. The molecular weights of final products were determined with a Shimadzu LC–MS/MS 8040 Liquid Chromatograph Mass Spectrometer using an ESI source. CEM SP Discover Microwave Synthesis Reactor was used for the microwave experiments.

General procedure for synthesis of compounds 4a–4g

Imidazo[1,2-*a*]pyrimidine-2-carbaldehyde [40] (100 mg, 0.68 mmol, 1.0 equiv.), 58 mg malononitrile (0.88 mmol, 1.3 equiv.), and enolizable compounds (0.88 mmol, 1.3 equiv.) were dissolved in 5 cm^3 water or a mixture of water:ethyl alcohol (4:1). Sodium carbonate (0.88 mmol, 93 mg, 1.3 equiv.) in 2 cm^3 water was added and the mixture was stirred at room temperature for various times (2–7 h). The reaction process was monitored with thin layer chromatography using different ratio of hexane:ethyl acetate mixture as solvent. After completion of the reaction, the mixture was poured into brine solution and stirred for 15 min. The resulting solid was suction filtered using filter paper with small pore size and washed with water. The pure products **4a**–**4g** were obtained by crystallization or washing with various solvents. Products were stored under argon atmosphere to prevent decomposition.

2-Amino-7-hydroxy-4-(imidazo[1,2-*a*]pyrimidin-2-yl)-4*H*-chromene-3-carbonitrile (4a, $C_{16}H_{11}N_5O_2$) Using resorcinol in water with 2 h reaction time. The pure product **4a** was obtained by crystallization with toluene/ethyl alcohol. Cream-colored solid; yield: 0.17 g (83%); m.p.: > 300 °C (dec.); ^{1}H NMR (600 MHz, DMSO-d_6): δ = 9.86 (1H, s), 8.52 (1H, dd, *J* = 3.90, 1.89 Hz), 8.48 (1H, dd, *J* = 6.88, 1.61 Hz), 7.63 (1H, s), 7.11 (2H, s), 7.04 (1H, dd, *J* = 4.1, 2.73 Hz), 6.73 (1H, t, *J* = 4.55 Hz), 6.46 (2H, m), 5.41 (1H, s) ppm; ^{13}C NMR (150 MHz, DMSO-d_6): δ = 161.41, 158.20, 150.00, 149.81, 148.58, 134.00, 132.59, 129.27, 125.14, 120.40, 113.17, 109.90, 109.23, 103.04, 52.30, 30.56 ppm; IR (ATR):

$\overline{\nu}$ = 3477, 3384, 3337, 3187, 3094, 2990, 2919, 2185, 1651, 1617, 1592, 1497, 1398, 1318, 1279, 1139, 1111, 1037, 911, 874, 839, 788, 773, 699, 667 cm^{-1}; MS: *m/z* (%) = 306 (M^+, 100), 279 (40), 206 (36), 180 (36).

2,7-Diamino-4-(imidazo[1,2-a]pyrimidin-2-yl)-4*H*-chromene-3-carbonitrile (4b, $C_{16}H_{12}N_6O$) Using 3-aminophenol in water:ethyl alcohol with 5 h reaction time. The pure product **4b** was obtained by washing with hot ethyl acetate. Brown solid; yield: 0.144 g (70%); m.p.: > 300 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.49 (1H, dd, *J* = 4.04, 1.91 Hz), 8.39 (1H, dd, *J* = 6.91, 1.90 Hz), 7.60 (1H, s), 7.00 (1H, dd, *J* = 6.89, 4.10 Hz), 6.97 (2H, s, broad), 6.53 (1H, d, *J* = 8.25 Hz), 6.24–6.20 (2H, m), 5.32 (2H, s, broad), 5.27 (1H, s) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 161.66, 150.10, 149.97, 149.94, 148.67, 133.96, 132.57, 128.83, 125.46, 120.63, 111.87, 109.22, 105.85, 100.68, 52.49, 30.75 ppm; IR (ATR): $\overline{\nu}$ = 3404, 3320, 3188, 3096, 3041, 3006, 2190, 1647, 1614, 1570, 1511, 1495, 1454, 1389, 1339, 1229, 1168, 1140, 1067, 1032, 973, 846, 787 cm^{-1}; MS: *m/z* (%) = 305 (M^+, 100), 279 (48), 157 (20).

2-Amino-7-hydroxy-4-(imidazo[1,2-a]pyrimidin-2-yl)-5-methyl-4*H*-chromene-3-carbonitrile (4c, $C_{17}H_{13}N_5O_2$) Using orcinol in water with 2 h reaction time. The pure product **4c** was obtained by washing with hot toluene. Cream-colored solid; yield: 0.175 g (81%); m.p.: 283–285 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.80 (s, 1H), 8.90 (dd, *J* = 7.05, 1.98 Hz, 1H), 8.47 (dd, *J* = 4.08, 1.94 Hz, 1H), 7.31 (s, 1H), 7.07 (dd, *J* = 6.90, 4.08 Hz, 1H), 6.95 (s, 2H), 6.36 (s, 1H), 6.30 (s, 1H), 5.28 (s, 1H), 2.15 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 161.16, 155.46, 150.04, 149.37, 147.57, 139.13, 133.28, 132.97, 127.79, 120.98, 112.16, 108.78, 107.64, 106.02, 54.36, 26.63, 21.37 ppm; IR (ATR): $\overline{\nu}$ = 3414, 3318, 3202, 3177, 3129, 3102, 3018, 2972–2863, 2186, 1645, 1580, 1504, 1398, 1337, 1298, 1257, 1146, 1079, 1050, 865, 829, 768, 726 cm^{-1}; MS: *m/z* (%) = 320 (M^+, 100), 310 (32), 279 (24), 171 (28).

2-Amino-6-chloro-7-hydroxy-4-(imidazo[1,2-a]pyrimidin-2-yl)-4*H*-chromene-3-carbonitrile (4d, $C_{16}H_{10}ClN_5O_2$) Using 4-chlororesorcinol in water:ethyl alcohol with 2 h reaction time. The pure product **4d** was obtained by washing with hot toluene/ethyl alcohol mixture. Light orange solid; yield: 0.155 g (67%); m.p.: > 300 °C (dec.); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.65 (1H, s), 8.54–8.51 (2H, m), 7.59 (1H, s), 7.12 (2H, s, broad), 7.04 (1H, dd, *J* = 6.82, 4.16 Hz), 6.90 (1H, *J* = 0.7 Hz, d), 6.66 (1H, s), 5.41 (1H, s) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 161.30, 153.78, 150.23, 148.70, 148.47, 134.19, 132.75, 129.00, 125.00, 120.23, 116.61, 111.64, 109.42, 104.49, 52.42, 30.43 ppm; IR (ATR): $\overline{\nu}$ = 3448, 3323, 3190, 3129, 3108, 2197, 1656, 1583, 1501, 1389, 1283, 1227, 1145, 1065, 876, 800, 785, 748, 700 cm^{-1}; MS: *m/z* (%) = 340 (M^+, 76), 327 (28), 300 (100), 279 (52).

2-Amino-7,8-dihydroxy-4-(imidazo[1,2-a]pyrimidin-2-yl)-4*H*-chromene-3-carbonitrile (4e, $C_{16}H_{11}N_5O_3$) Using pyrogallol in water with 2 h reaction time. The pure product **4e** was obtained by washing with hot toluene. Brown solid; yield: 0.173 g (79%); m.p.: > 195 °C (dec.); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.49 (dd, *J* = 4.08, 1.96 Hz, 1H), 8.43 (dd, *J* = 6.92, 1.97 Hz, 1H), 7.60 (s, 1H), 7.01 (dd, *J* = 6.89, 4.1 Hz, 1H), 6.95 (s, 2H), 6.44 (d, *J* = 8.4 Hz, 1H), 6.15 (d, *J* = 8.4 Hz, 1H), 5.37 (s, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 161.71, 150.01, 148.67, 146.20, 139.05, 134.00, 133.90, 132.65, 125.57, 120.54, 117.10, 112.41, 111.40, 109.25, 52.51, 31.08 ppm; IR (ATR): $\overline{\nu}$ = 3363, 3179, 3087, 2188, 1648, 1611, 1589, 1519, 1485, 1400, 1300, 1203, 1152, 1084, 1062, 944, 874, 782, 762, 719 cm^{-1}; MS: *m/z* (%) = 322 (M^+, 100), 310 (16), 279 (40), 180 (30).

2-Amino-4-(imidazo[1,2-a]pyrimidin-2-yl)-4*H*-benzo[*h*]-chromene-3-carbonitrile (4f, $C_{20}H_{13}N_5O$) Using 1-naphthol in water:ethyl alcohol with 7 h reaction time. The pure product **4f** was obtained by crystallization with toluene/ethyl alcohol mixture. Light brown solid; yield: 0.135 g (59%); m.p.: > 209 °C (dec.); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.58 (1H, dd, *J* = 6.93, 1.94 Hz), 8.50 (1H, dd, *J* = 4.12, 1.91 Hz), 8.26 (1H, d, *J* = 7.96 Hz), 7.88 (1H, d, *J* = 7.92 Hz), 7.66 (1H, s), 7.60–7.56 (2H, m), 7.33 (2H, s, broad), 7.08 (1H, m), 7.02–6.99 (2H, m), 5.70 (1H, s) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 161.37, 150.23, 148.73, 144.05, 134.51, 133.67, 132.71, 129.43, 128.74, 127.42, 125.85, 125.42, 125.05, 124.91, 123.28, 121.39, 114.56, 109.46, 52.62, 31.52 ppm; IR (ATR): $\overline{\nu}$ = 3350, 3306, 3149, 3055, 2188, 1655, 1616, 1572, 1516, 1494, 1371, 1260, 1187, 1143, 1104, 797, 764, 732 cm^{-1}; MS: *m/z* (%) = 340 (M^+, 100), 329 (32), 300 (24), 279 (66).

2-Amino-4-(imidazo[1,2-a]pyrimidin-2-yl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4g, $C_{18}H_{17}N_5O_2$) Using dimedone in water:ethyl alcohol with 3 h reaction time. After completion of the reaction, the mixture was poured into brine solution but solid formation was not observed. Therefore, the mixture was extracted with ethyl acetate (3 × 15 cm^3), the organic phase was washed with water, dried with anhydrous Na_2SO_4 and evaporated in vacuo. The oily crude product was solidified using diethylether and crystallized with toluene to give **4g**. Light orange solid; yield: 0.136 g (60%); m.p.: 145–149 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.09 (dd, *J* = 6.99, 1.88 Hz, 1H), 8.49 (dd, *J* = 4.06, 1.90 Hz, 1H), 7.44 (s, 1H), 7.13 (s, 2H), 7.09 (dd, *J* = 6.92, 4.08 Hz, 1H), 4.95 (s, 1H), 2.50 (s, 2H),

2.19, 2.10 (s, 2H), 1.00 (s, 3H), 0.91 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 196.86, 163.33, 159.28, 149.75, 147.62, 133.71, 133.09, 127.48, 120.11, 111.37, 108.80, 55.96, 50.40, 32.36, 28.59, 27.47, 25.18 ppm; IR (ATR): $\overline{v}$ = 3303, 3106, 2958, 2871, 2191, 1680, 1658, 1616, 1512, 1429, 1359, 1249, 1215, 1141, 1041, 765 cm^{-1}; MS: *m*/*z* (%) = 336 (M^+, 100), 327 (32), 310 (24), 279 (60).

Acknowledgements I am grateful to Prof. Dr. Mehmet AY for his support.

References

1. Sabry NM, Mohamed HM, Khattab ESAEH, Motlaq SS, El-Agrody AM (2011) Eur J Med Chem 46:765
2. Chung ST, Huang WH, Huang CK, Liu FC, Huang RY, Wu CC, Lee AR (2016) Res Chem Intermed 42:1195
3. Khoobi M, Alipour M, Sakhteman A, Nadri H, Moradi A, Ghandi M, Emami S, Foroumadi A, Shafie A (2013) Eur J Med Chem 68:260
4. Smith CW, Bailey JM, Billingham MEJ, Chandrasekhar S, Dell CP, Harvey AK, Hicks CA, Kingston AE, Wishart GN (1995) Bioorg Med Chem Lett 5:2783
5. Yousefi MR, Goli-Jolodar O, Shirini F (2018) Bioorg Chem 81:326
6. Huynh THV, Abrahamsen B, Madsen KK, Gonzalez-Franquesa A, Jensen AA, Bunch L (2012) Bioorg Med Chem 20:6831
7. Makawana JA, Mungra DC, Patel MP, Patel RG (2011) Bioorg Med Chem Lett 21:6166
8. Thanh ND, Hai DS, Ngoc Bich VT, Hien PTT, Duyen NTK, Mai NT, Dung TT, Toan VN, Van HTK, Dang LH, Toan DN, Van TTT (2019) Eur J Med Chem 167:454
9. Kumar D, Reddy VB, Sharad S, Dube U, Kapur S (2009) Eur J Med Chem 44:3805
10. Kidwai M, Poddar R, Bhardwaj S, Singh S, Luthra PM (2010) Eur J Med Chem 45:5031
11. Mirjalili BBF, Zamani L, Zomorodian K, Khabnadideh S, Haghighijoo Z, Malakotikhah Z, Mousavi SAA, Khojasteh S (2016) J Mol Struct 1116:102
12. Surpur MP, Kshirsagar S, Samant SD (2009) Tetrahedron Lett 50:719
13. Safari J, Heydarian M, Zarnegar Z (2017) Arab J Chem 10:2994
14. Heydari R, Shahraki R, Hossaini M (2017) Res Chem Intermed 43:4611
15. Kiyani H (2017) Res Chem Intermed 43:6639
16. Behbahani FK, Mehraban S (2015) J Korean Chem Soc 59:284
17. Pagore VP, Tekale SU, Rupnar BD, Pawar RP (2015) J Chem Pharm Res 7:1057
18. Cherif M, Debbabi M, Chortani S, Romdhane A, Jannet HB (2018) Turk J Chem 42:1623
19. Aeluri R, Alla M, Polepalli S, Jain N (2015) Eur J Med Chem 100:18
20. Kamal A, Reddy JS, Ramaiah MJ, Dastagiri D, Bharathi EV, Prem Sagar MV, Pushpavalli SNCVL, Ray P, Pal-Bhadra M (2010) MedChemComm 1:355
21. Mantipally M, Gangireddya MR, Gundla R, Badavath VN, Mandhaa SR, Maddipati VC (2019) Bioorg Med Chem Lett 29:2248
22. Spitzer WA, Victor F, Don Pollock G, Scott Hayes J (1988) J Med Chem 31:1590
23. Rao NS, Kistareddy C, Balram B, Ram B (2012) Pharm Chem 4:2408
24. Al-Tel TH, Al-Qawasmeh RA (2010) Eur J Med Chem 45:5848
25. Gómez-García O, Andrade-Pavón D, Campos-Aldrete E, Ballinas-Indilí R, Méndez-Tenorio A, Villa-Tanaca L, Álvarez-Toledano C (2018) Molecules 23:1
26. Gueiffier A, Lhassani M, Elhakmaoui A, Snoeck R, Andrei G, Chavignon O, Teulade JC, Kerbal A, Essassi EM, Debouzy JC, Witvrouw M, Blache Y, Balzarini J, De Clercq E, Chapat JP (1996) J Med Chem 39:2856
27. Zhou JP, Ding YW, Zhang HB, Xu L, Dai Y (2008) Chin Chem Lett 19:669
28. Moog C, Wick A, Le Ber P, Kirn A, Aubertin AM (1994) Antiviral Res 24:275
29. Sanfilippo PJ, Urbanski M, Press JB, Dubinsky B, Moore JB (1988) J Med Chem 31:2221
30. Rupert KC, Henry JR, Dodd JH, Wadsworth SA, Cavender DE, Olini GC, Fahmy B, Siekierka JJ (2003) Bioorg Med Chem Lett 13:347
31. Goel R, Luxami V, Paul K (2015) RSC Adv 5:81608
32. Al-Lami N, Amer Z, Ali RA (2018) J Pharm Sci Res 10:3344
33. Velázquez-Olvera S, Salgado-Zamora H, Velázquez-Ponce M, Campos-Aldrete E, Reyes-Arellano A, Pérez-González C (2012) Chem Cent J 6:1
34. Verma P, Pal S, Chauhan S, Mishra A, Sinha I, Singh S, Srivastava V (2020) J Mol Struct 1203:127410
35. Clements-Jewery S, Danswan G, Gardner CR, Matharu SS, Murdoch R, Tully WR, Westwood R (1988) J Med Chem 31:1220
36. Feely M, Boyland P, Picardo A, Cox A, Gent JP (1989) Eur J Pharmacol 164:377
37. Tully WR, Gardner CR, Gillespie RJ, Westwood R (1991) J Med Chem 34:2060
38. Levi L, Müller TJJ (2016) Chem Soc Rev 45:2825
39. Bhaskaruni SVHS, Maddila S, Gangu KK, Jonnalagadda SB (2020) Arab J Chem 13:1142
40. Binh Nguyen T, Anh Nguyen L, Corbin M, Retailleau P, Ermolenko L, Al-Mourabit A (2018) Eur J Org Chem 2018:5861
41. Kethireddy S, Eppakayala L, Maringanti TC (2015) Chem Cent J 9:2