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Synthesis and antimicrobial studies of some novel series of fused naphthopyranotetrazole derivatives

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Abstract A series of novel fused tetrazolylbenzo[*h*]chromenes **3a–f**, **4a–f** and **5a–f** were prepared starting from 2-amino-benzo[*h*]chromene-3-carbonitrile **1a–f**. All structures of the newly synthesized compounds were confirmed by IR, NMR, mass spectral studies, and elemental analyses. The newly synthesized compounds were screened for their antibacterial and antifungal activity. Some of the derivatives have exhibited promising biological activity.

Keywords Benzo[*h*]chromene · Fused tetrazole · Pyrimidine · Diazepine · Antimicrobial activity

Introduction

Chromene annulated heterocyle derivatives represent an important class of oxygen-containing heterocycles, being the main components in many of naturally occurring products, and having a wide spectrum of biological and pharmacological properties, like antimicrobial [1], antiviral, antileishmanial [2], mutagenicity [3], antiproliferative [4], antitumor [5], anticancer [6], and central nervous system activity [7]. Some of them are widely employed as cosmetics, pigments [8], and potential biodegradable agrochemicals [9].

Tetrazoles constitute an interesting class of heterocyclic compounds that have a wide range of applications. These nitrogen-rich heterocycles have been used as a metabolically stable isosteric replacement for the carboxylic acid moiety [10], as a *cis*-peptide bond mimetic [11, 12], as a precursor to other heterocycles [13], in high-energy compounds [14], and as a coordinating group in directed *ortho*-metalation [15–17]. They are also resistant to metabolic degradation as well as towards

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chemical oxidants [18]. Recently, several biologically relevant substances incorporating a tetrazole moiety have been developed. For example, Losartan is an angiotensin II antagonist, which has been used to treat hypertension [19, 20]. Pentylenetetrazole has been extensively used in models for anxiety [21, 22]. Some tetrazoles show affinity to benzodiazepine receptors [23].

On the other hand, pyrimidine scaffolds have been potentially important pharmacophores of many bioactive molecules [25]. They are known to possess antitubercular, antimicrobial [24], antiplatelet [26], antiinflammatory [27], antigenotoxic [28], antiallergic [29], anti-proliferative, and apoptotic activity [30].

It is evident from the literature that diazepine derivatives have been found to exhibit various pharmacological activities. They are widely used as anticonvulsants, antianxiolitics, analgesics, sedatives, antidepressives, and hypnotic agents [31–35].

Prompted by these observations, and as part of our research program aimed at developing new biologically active heterocycles [36], in this paper, we designed and synthesized a series of novel condensed systems (benzopyran-containing tetrazoles fused with pyrimidine and diazepine) that combine these pharmacophores in a ring to give a compact and planar structure, which were evaluated for their antimicrobial activity.

Experimental

Melting points were recorded on a Stuart SMP30 melting point apparatus and were uncorrected. Column chromatography was performed using silica–gel (100–200 mesh size) purchased from Thomas Baker, and thin layer chromatography (TLC) was carried out using aluminium sheets pre-coated with silica gel $60F_{254}$ purchased from Merck. IR spectra (KBr) were obtained using a PerkinElmer Spectrum100 FT-IR Spectrometer. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker WM-400 spectrometer in DMSO-d_6 with TMS as an internal standard. Mass spectra (ESI) were carried out on a JEOL SX-102 spectrometer. CHN analysis was done by Carlo Erba EA 1108 automatic elemental analyzer. The chemicals and solvents used were of commercial grade and were used without further purification unless otherwise stated.

General procedure for the synthesis of 4-aryl-3-(1*H*-tetrazol-5-yl)-4*H*-benzo[*h*]chromen-2-amines (2a–f)

To a mixture of compound **1a–f** (10 mmol) in DMF (40 mL), sodium azide (12 mmol), and NH_4Cl (12 mmol) were added and the reaction mixture was stirred at 120 °C for 7 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature, poured into ice-cold water (100 mL), and the solid separated was filtered, washed with water, dried, and purified by column chromatography on silica gel using hexane/ethyl acetate (7:3) as eluent to afford compound **2a–f**.

4-Phenyl-3-(1H-tetrazol-5-yl)-4H-benzo[h]chromen-2-amine (2a)

Orange solid, yield: 68 %; mp: 191–194 °C. IR (KBr, cm^{-1}): 3,471, 3,291, 3,222, 2,967, 1,610, 1,597, 1,517, 1,491, 1,402, 1,349, 1,326, 1,200, 1,076. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 4.90 (s, 1H, H-4), 7.10–7.34 (m, 8H, ArH + NH_2), 7.55–7.67 (m, 3H, ArH), 7.89 (d, 1H, ArH), 8.24 (d, 1H, ArH), 10.51 (s, 1H, NH) ppm. ^{13}C NMR (DMSO-d_6, 100 MHz): δ 40.96, 89.30, 120.57, 120.73, 122.78, 123.90, 126.23, 126.67, 126.76, 126.93, 127.68, 128.71, 132.70, 142.76, 145.71, 158.93, 161.20 ppm. ESI–MS (*m/z*): 342 $(M+1)^+$. Anal. Calcd for $C_{20}H_{15}N_5O$: C, 70.37; H, 4.43; N, 20.52. Found: C, 70.49; H, 4.50; N, 20.41.

4-(4-Chlorophenyl)-3-(1H-tetrazol-5-yl)-4H-benzo[h]chromen-2-amine (2b)

Brown solid, yield: 64 %; mp: 162–164 °C. IR (KBr, cm^{-1}): 3,432, 3,372, 3,242, 2,983, 1,600, 1,586, 1,508, 1,492, 1,392, 1,337, 1,311, 1,209, 1,072. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 4.86 (s, 1H, H-4), 7.01–7.20 (m, 3H, ArH + NH_2), 7.39–7.53 (m, 7H, ArH), 7.81 (d, 1H, ArH), 8.19 (d, 1H, ArH), 10.46 (s, 1H, NH) ppm. ^{13}C NMR (DMSO-d_6, 100 MHz): δ 40.93, 89.76, 120.47, 120.78, 123.71, 124.82, 125.97, 126.82, 126.94, 127.80, 129.05, 129.48, 133.27, 133.38, 142.93, 145.30, 159.00, 161.32 ppm. ESI–MS (*m/z*): 376 $(M+1)^+$. Anal. Calcd for $C_{20}H_{14}ClN_5O$: C, 63.92; H, 3.75; N, 18.64. Found: C, 63.83; H, 3.69; N, 18.75.

4-(4-Fluorophenyl)-3-(1H-tetrazol-5-yl)-4H-benzo[h]chromen-2-amine (2c)

Yellow solid, yield: 66 %; mp: 181–183 °C. IR (KBr, cm^{-1}): 3,446, 3,397, 3,221, 2,972, 1,609, 1,593, 1,509, 1,490, 1,400, 1,342, 1,322, 1,208, 1,071. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 4.87 (s, 1H, H-4), 7.03–7.24 (m, 3H, ArH + NH_2), 7.44–7.58 (m, 7H, ArH), 7.81 (d, 1H, ArH), 8.11 (d, 1H, ArH), 10.37 (s, 1H, NH) ppm. ^{13}C NMR (DMSO-d_6, 100 MHz): δ 41.17, 89.68, 120.51, 120.83, 123.18, 124.74, 125.93, 126.77, 126.98, 127.71, 129.13, 129.56, 133.44, 133.67, 142.91, 145.21, 159.11, 161.41 ppm. ESI–MS (*m/z*): 360 $(M+1)^+$. Anal. Calcd for $C_{20}H_{14}FN_5O$: C, 66.85; H, 3.93; N, 19.49. Found: C, 66.97; H, 3.81; N, 19.56.

4-(4-Methylphenyl)-3-(1H-tetrazol-5-yl)-4H-benzo[h]chromen-2-amine (2d)

Yellow solid, yield: 64 %; mp: 170–172 °C. IR (KBr, cm^{-1}): 3,391, 3,298, 3,202, 2,969, 1,602, 1,594, 1,519, 1,494, 1,410, 1,351, 1,328, 1,204, 1,078. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.32 (s, 3H, CH_3), 4.84 (s, 1H, H-4), 7.04-7.37 (m, 7H, ArH + NH_2), 7.48-7.60 (m, 3H, ArH), 7.80 (d, 1H, ArH), 8.16 (d, 1H, ArH), 10.48 (s, 1H, NH) ppm. ^{13}C NMR (DMSO-d_6, 100 MHz): δ 21.72, 41.31, 89.63, 120.01, 120.73, 123.35, 124.93, 126.71, 126.93, 127.10, 128.11, 128.41, 128.94, 130.38, 133.73, 137.44, 142.08, 159.04, 161.36 ppm. ESI–MS (*m/z*): 356 $(M+1)^+$. Anal. Calcd for $C_{21}H_{17}N_5O$: C, 70.97; H, 4.82; N, 19.71. Found: C, 70.88; H, 4.70; N, 19.83.

4-(4-Methoxyphenyl)-3-(1H-tetrazol-5-yl)-4H-benzo[h]chromen-2-amine (2e)

Orange solid, yield: 61 %; mp: 154–156 °C. IR (KBr, cm^{-1}): 3,383, 3,277, 3,226, 2,982, 1,604, 1,595, 1,512, 1,493, 1,411, 1,341, 1,321, 1,203, 1,072. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.84 (s, 3H, OCH_3), 4.88 (s, 1H, H-4), 7.03–7.35 (m, 7H, ArH + NH_2), 7.50-7.59 (m, 3H, ArH), 7.81 (d, 1H, ArH), 8.19 (d, 1H, ArH), 10.32 (s, 1H, NH) ppm. ^{13}C NMR (DMSO-d_6, 100 MHz): δ 41.79, 55.48, 89.91, 114.74, 121.17, 123.62, 124.83, 126.62, 126.91, 127.23, 127.61, 128.54, 128.82, 129.67, 133.76, 144.82, 158.91, 159.25, 161.77 ppm. ESI–MS (*m/z*): 372 $(M+1)^+$. Anal. Calcd for $C_{21}H_{17}N_5O_2$: C, 67.91; H, 4.61; N, 18.86. Found: C, 67.84; H, 4.70; N, 18.94.

4-(3-Nitrophenyl)-3-(1H-tetrazol-5-yl)-4H-benzo[h]chromen-2-amine (2f)

Brown solid, yield: 58 %; mp: 187–189 °C. IR (KBr, cm^{-1}): 3,461, 3,394, 3,221, 2,977, 1,605, 1,591, 1,511, 1,492, 1,407, 1,343, 1,322, 1,209, 1,075. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 5.08 (s, 1H, H-4), 7.02 (d, 1H, ArH), 7.30–7.38 (m, 5H, ArH + NH_2), 7.48 (t, 1H, ArH), 7.54 (d, 1H, ArH), 7.74 (d, 1H, ArH), 8.03 (d, 1H, ArH), 8.12 (s, 1H, ArH), 8.22 (d, 1H, ArH), 10.61 (s, 1H, NH) ppm. ^{13}C NMR (DMSO-d_6, 100 MHz): δ 42.11, 89.98, 119.72, 121.29, 122.67, 123.38, 123.94, 125.41, 125.86, 127.66, 127.84, 128.25, 130.41, 133.85, 134.81, 144.72, 146.88, 149.25, 159.43, 161.96 ppm. ESI–MS (*m/z*): 387 $(M+1)^+$. Anal. Calcd for $C_{20}H_{14}N_6O_3$: C, 62.17; H, 3.65; N, 21.75. Found: C, 62.26; H, 3.71; N, 21.66.

General procedure for the synthesis of fused naphthopyrano[3,2-*e*]tetrazolo[2,3-c]pyrimidin-5-thiones (3a–f)

A mixture of compound **2a**–**f** (2 mmol) and carbon disulfide (2 mmol) in pyridine (10 mL) were refluxed on a water bath for 16 h. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature then poured into ice-cold water (20 mL) and neutralized with hydrochloric acid (1:1). The solid obtained was filtered, washed with water, dried, and recrystallized from ethanol to afford compound **3a**–**f**.

14-Phenyl-5,6-dihydro-5H,14H-naphtho[1′,2′:5,6]pyrano[3,2-e][1–4]tetrazolo[2,3-c]pyrimidin-5-thione (3a)

White solid, yield: 64 %; mp: 175–177 °C. IR (KBr, cm^{-1}): 3,411, 1,592, 1,546, 1,489, 1,468, 1,412, 1,178, 1,090. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 4.90 (s, 1H, H-4), 7.10–7.35 (m, 7H, ArH), 7.55–7.65 (m, 2H, ArH), 7.88 (d, 1H, ArH), 8.25 (d, 1H, ArH), 10.43 (s, 1H, NH) ppm. ^{13}C NMR (DMSO-d_6, 100 MHz): δ 40.91, 89.41, 120.47, 120.67, 122.74, 123.84, 126.17, 126.61, 126.71, 126.87, 127.62, 128.65, 132.65, 142.72, 145.65, 159.33, 161.92, 189.51 ppm. ESI–MS (*m/z*): 384 $(M+1)^+$. Anal. Calcd for $C_{21}H_{13}N_5OS$: C, 65.78; H, 3.42; N, 18.27. Found: C, 65.87; H, 3.51; N, 18.20.

14-(4-Chlorophenyl)-5,6-dihydro-5H,14H-naphtho[1′,2′:5,6]pyrano[3,2-e][1–4]tetrazolo[2,3-c]pyrimidin-5-thione (3b)

White solid, yield: 61 %; mp: 198–200 °C. IR (KBr, cm^{-1}): 3,387, 1,590, 1,534, 1,477, 1,464, 1,417, 1,172, 1,087. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 4.84 (s, 1H, H-4), 6.99 (d, 1H, ArH), 7.18–7.33 (m, 4H, ArH), 7.52–7.58 (m, 3H, ArH), 7.80 (d, 1H, ArH), 8.14 (d, 1H, ArH), 10.32 (s, 1H, NH) ppm. ^{13}C NMR (DMSO-d_6, 100 MHz): δ 41.04, 89.71, 120.75, 120.88, 123.13, 124.79, 125.81, 126.37, 126.87, 127.73, 129.32, 129.85, 133.32, 133.41, 142.84, 145.41, 159.48, 162.04, 189.72 ppm. ESI–MS (*m/z*): 418 $(M+1)^+$. Anal. Calcd for $C_{21}H_{12}ClN_5OS$: C, 60.36; H, 2.89; N, 16.76. Found: C, 60.43; H, 2.71; N, 16.83.

14-(4-Fluorophenyl)-5,6-dihydro-5H,14H-naphtho[1′,2′:5,6]pyrano[3,2-e][1–4]tetrazolo[2,3-c]pyrimidin-5-thione (3c)

White solid, yield: 62 %; mp: 212–214 °C. IR (KBr, cm^{-1}): 3,394, 1,594, 1,532, 1,482, 1,461, 1,411, 1,175, 1,091. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 4.88 (s, 1H, H-4), 7.04 (d, 1H, ArH), 7.16–7.31 (m, 4H, ArH), 7.54–7.60 (m, 3H, ArH), 7.82 (d, 1H, ArH), 8.16 (d, 1H, ArH), 10.36 (s, 1H, NH) ppm. ^{13}C NMR (DMSO-d_6, 100 MHz): δ 41.32, 89.76, 120.58, 120.89, 123.32, 124.98, 125.34, 126.72, 126.91, 127.89, 129.24, 129.76, 133.24, 133.62, 142.76, 145.53, 159.63, 162.21, 189.83 ppm. ESI–MS (*m/z*): 402 $(M+1)^+$. Anal. Calcd for $C_{21}H_{12}FN_5OS$: C, 62.83; H, 3.01; N, 17.45. Found: C, 62.97; H, 3.12; N, 17.36.

14-(4-Methylphenyl)-5,6-dihydro-5H,14H-naphtho[1′,2′:5,6]pyrano[3,2-e][1–4]tetrazolo[2,3-c]pyrimidin-5-thione (3d)

White solid, yield: 60 %; mp: 162–164 °C. IR (KBr, cm^{-1}): 3,389, 1,590, 1,549, 1,492, 1,463, 1,410, 1,180, 1,087. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.33 (s, 3H, CH_3), 4.80 (s, 1H, H-4), 7.02 (d, 1H, ArH), 7.14–7.36 (m, 4H, ArH), 7.46–7.59 (m, 3H, ArH), 7.81 (d, 1H, ArH), 8.19 (d, 1H, ArH), 10.39 (s, 1H, NH) ppm. ^{13}C NMR (DMSO-d_6, 100 MHz): δ 21.84, 41.38, 89.71, 120.67, 121.13, 123.54, 124.81, 126.67, 126.89, 127.23, 128.17, 128.47, 128.84, 130.42, 133.86, 137.52, 142.13, 159.38, 162.38, 189.87 ppm. ESI–MS (*m/z*): 398 $(M+1)^+$. Anal. Calcd for $C_{22}H_{15}N_5OS$: C, 66.48; H, 3.80; N, 17.62. Found: C, 66.34; H, 3.71; N, 17.77.

14-(4-Methoxyphenyl)-5,6-dihydro-5H,14H-naphtho[1′,2′:5,6]pyrano[3,2-e][1–4]tetrazolo[2,3-c]pyrimidin-5-thione (3e)

White solid, yield: 54 %; mp: 144–146 °C. IR (KBr, cm^{-1}): 3,403, 1,594, 1,532, 1,481, 1,460, 1,417, 1,167, 1,091. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.87 (s, 3H, OCH_3), 4.96 (s, 1H, H-4), 7.00 (d, 1H, ArH), 7.23–7.45 (m, 4H, ArH), 7.52–7.60 (m, 3H, ArH), 7.83 (d, 1H, ArH), 8.14 (d, 1H, ArH), 10.41 (s, 1H, NH) ppm. ^{13}C NMR (DMSO-d_6, 100 MHz): δ 41.84, 55.56, 89.94, 114.82, 121.27, 123.54, 124.87, 126.73, 126.94, 127.36, 127.74, 128.41, 128.61, 129.64, 133.78, 144.80, 159.82,

160.02, 162.52, 189.97 ppm. ESI–MS (*m/z*): 414 $(M+1)^+$. Anal. Calcd for $C_{22}H_{15}N_5O_2S$: C, 63.91; H, 3.66; N, 16.94. Found: C, 63.82; H, 3.78; N, 16.87.

14-(3-Nitrophenyl)-5,6-dihydro-5H,14H-naphtho[1′,2′:5,6]pyrano[3,2-e][1–4]tetrazolo[2,3-c]pyrimidin-5-thione (3f)

White solid, yield: 52 %; mp: 223–226 °C. IR (KBr, cm^{-1}): 3,413, 1,596, 1,537, 1,481, 1,462, 1,410, 1,181, 1,088. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 5.08 (s, 1H, H-4), 6.98 (d, 1H, ArH), 7.34–7.48 (m, 3H, ArH), 7.51 (t, 1H, ArH), 7.58 (d, 1H, ArH), 7.81 (d, 1H, ArH), 8.04 (d, 1H, ArH), 8.14 (s, 1H, ArH), 8.23 (d, 1H, ArH), 10.52 (s, 1H, NH) ppm. ^{13}C NMR (DMSO-d_6, 100 MHz): δ 41.98, 90.08, 119.81, 121.42, 122.78, 123.84, 123.51, 125.63, 125.94, 127.69, 127.81, 128.43, 130.48, 133.91, 134.93, 144.77, 146.93, 149.41, 159.94, 163.19, 190.14 ppm. ESI–MS (*m/z*): 429 $(M+1)^+$. Anal. Calcd for $C_{21}H_{12}N_6O_3S$: C, 58.87; H, 2.82; N, 19.62. Found: C, 58.94; H, 2.74; N, 19.56.

General procedure for the synthesis of fused naphthopyrano[3,2-*e*]tetrazolo[2,3-*c*]pyrimidines (4a–f)

To a mixture of compound **2a–f** (2 mmol) and benzaldehyde (2 mmol) in methanol (10 mL), conc. HCl (0.5 mL) was added and the reaction mixture was refluxed for 20 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature and neutralized with saturated sodium bicarbonate solution, and the solid separated was filtered, washed with water, dried, and recrystallized from ethanol to afford compound **4a–f**.

5,14-Diphenyl-6-hydro-5H,14H-naphtho[1′,2′:5,6]pyrano[3,2-e][1–4]tetrazolo[2,3-c]pyrimidine (4a)

White solid, yield: 66 %; mp: 275–278 °C. IR (KBr, cm^{-1}): 3,413, 1,617, 1,537, 1,493, 1,453, 1,379, 1,260, 1,154. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 5.30 (s, 1H, H-4), 5.81 (s, 1H, pyrimidine CH), 6.93 (d, 1H, ArH), 7.36–7.68 (m, 12H, ArH), 7.84–7.97 (m, 2H, ArH), 8.30 (d, 1H, ArH), 10.24 (s, 1H, NH) ppm. ^{13}C NMR (DMSO-d_6, 100 MHz): δ 41.10, 64.12, 88.32, 120.32, 120.70, 122.71, 123.35, 123.84, 125.56, 125.65, 125.73, 126.22, 126.68, 127.63, 128.77, 130.81, 132.70, 133.75, 139.17, 142.70, 160.02, 162.73 ppm. ESI–MS (*m/z*): 430 $(M+1)^+$. Anal. Calcd for $C_{27}H_{19}N_5O$: C, 75.51; H, 4.46; N, 16.31. Found: C, 75.63; H, 4.53; N, 16.20.

14-(4-Chlorophenyl)-5-phenyl-6-hydro-5H,14H-naphtho[1′,2′:5,6]pyrano[3,2-e][1–4]tetrazolo[2,3-c]pyrimidine (4b)

White solid, yield: 63 %; mp: 214–216 °C. IR (KBr, cm^{-1}): 3,389, 1,600, 1,532, 1,495, 1,431, 1,372, 1,263, 1,142. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 5.19 (s, 1H, pyran CH), 5.88 (s, 1H, pyrimidine CH), 7.02–7.21 (m, 5H, ArH), 7.38–7.60 (m, 8H, ArH), 7.82 (d, 1H, ArH), 8.17 (d, 1H, ArH), 10.32 (s, 1H, NH) ppm. ^{13}C NMR

(DMSO-d_6, 100 MHz): δ 41.32, 64.41, 88.38, 120.63, 120.76, 123.24, 124.86, 125.72, 126.41, 126.53, 127.12, 127.71, 128.47, 128.72, 129.43, 129.82, 133.24, 133.61, 139.13, 142.71, 145.84, 159.78, 162.42 ppm. ESI–MS (*m/z*): 464 $(M+1)^+$. Anal. Calcd for $C_{27}H_{18}ClN_5O$: C, 69.90; H, 3.91; N, 15.10. Found: C, 69.83; H, 3.82; N, 15.23.

14-(4-Fluorophenyl)-5-phenyl-6-hydro-5H,14H-naphtho[1′,2′:5,6]pyrano[3,2-e][1–4]tetrazolo[2,3-c]pyrimidine (4c)

White solid, yield: 60 %; mp: 172–175 °C. IR (KBr, cm^{-1}): 3,383, 1,591, 1,529, 1,490, 1,431, 1,368, 1,264, 1,153. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 5.14 (s, 1H, pyran CH), 5.92 (s, 1H, pyrimidine CH), 7.01–7.26 (m, 5H, ArH), 7.47–7.62 (m, 8H, ArH), 7.81 (d, 1H, ArH), 8.20 (d, 1H, ArH), 10.34 (s, 1H, NH) ppm. ^{13}C NMR (DMSO-d_6, 100 MHz): δ 41.47, 64.72, 88.41, 120.47, 120.94, 123.24, 124.90, 125.44, 126.28, 126.69, 127.32, 127.78, 128.31, 128.86, 129.35, 129.68, 133.42, 133.87, 139.17, 142.58, 145.47, 159.72, 162.31 ppm. ESI–MS (*m/z*): 448 $(M+1)^+$. Anal. Calcd for $C_{27}H_{18}FN_5O$: C, 72.47; H, 4.05; N, 15.65. Found: C, 72.53; H, 4.13; N, 15.56.

14-(4-Methylphenyl)-5-phenyl-6-hydro-5H,14H-naphtho[1′,2′:5,6]pyrano[3,2-e][1–4]tetrazolo[2,3-c]pyrimidine (4d)

White solid, yield: 61 %; mp: 185–188 °C. IR (KBr, cm^{-1}): 3,397, 1,588, 1,531, 1,484, 1,437, 1,382, 1,263, 1,150. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.35 (s, 3H, CH_3), 5.17 (s, 1H, pyran CH), 5.90 (s, 1H, pyrimidine CH), 6.96 (d, 1H, ArH), 7.12–7.31 (m, 4H, ArH), 7.44–7.61 (m, 8H, ArH), 7.80 (d, 1H, ArH), 8.16 (d, 1H, ArH), 10.30 (s, 1H, NH) ppm. ^{13}C NMR (DMSO-d_6, 100 MHz): δ 21.66, 41.38, 64.61, 89.07, 120.61, 121.18, 123.54, 124.47, 126.53, 126.81, 126.94, 127.23, 127.74, 128.19, 128.53, 128.87, 129.62, 130.31, 133.83, 137.41, 138.53, 142.14, 159.81, 162.38 ppm. ESI–MS (*m/z*): 444 $(M+1)^+$. Anal. Calcd for $C_{28}H_{21}N_5O$: C, 75.83; H, 4.77; N, 15.79. Found: C, 75.74; H, 4.71; N, 15.87.

14-(4-Methoxyphenyl)-5-phenyl-6-hydro-5H,14H-naphtho[1′,2′:5,6]pyrano[3,2-e][1–4]tetrazolo[2,3-c]pyrimidine (4e)

White solid, yield: 57 %; mp: 196–198 °C. IR (KBr, cm^{-1}): 3,389, 1,588, 1,523, 1,484, 1,451, 1,370, 1,257, 1,148. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.89 (s, 3H, OCH_3), 5.20 (s, 1H, pyran CH), 6.02 (s, 1H, pyrimidine CH), 7.05 (d, 1H, ArH), 7.21–7.63 (m, 12H, ArH), 7.62 (d, 1H, ArH), 8.21 (d, 1H, ArH), 10.39 (s, 1H, NH) ppm. ^{13}C NMR (DMSO-d_6, 100 MHz): δ 41.72, 55.59, 65.19, 89.18, 114.79, 121.36, 123.71, 124.88, 126.32, 126.67, 126.89, 127.34, 127.68, 127.93, 128.37, 128.74, 128.89, 129.71, 133.63, 138.92, 144.86, 159.87, 160.23, 162.68 ppm. ESI–MS (*m/z*): 460 $(M+1)^+$. Anal. Calcd for $C_{28}H_{21}N_5O_2$: C, 73.19; H, 4.61; N, 15.24. Found: C, 73.28; H, 4.54; N, 15.35.

14-(3-Nitrophenyl)-5-phenyl-6-hydro-5H,14H-naphtho[1′,2′:5,6]pyrano[3,2-e][1–4]tetrazolo[2,3-c]pyrimidine (4f)

White solid, yield: 52 %; mp: 242–244 °C. IR (KBr, cm^{-1}): 3,419, 1,598, 1,532, 1,481, 1,453, 1,372, 1,261, 1,153. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 5.34 (s, 1H, pyran CH), 6.13 (s, 1H, pyrimidine CH), 7.01 (d, 1H, ArH), 7.36–7.47 (m, 8H, ArH), 7.50 (t, 1H, ArH), 7.56 (d, 1H, ArH), 7.77 (d, 1H, ArH), 8.01 (d, 1H, ArH), 8.10 (s, 1H, ArH), 8.27 (d, 1H, ArH), 10.47 (s, 1H, NH) ppm. ^{13}C NMR (DMSO-d_6, 100 MHz): δ 42.07, 65.31, 89.36, 119.84, 121.17, 122.59, 123.22, 123.87, 124.53, 125.94, 126.37, 127.42, 127.74, 127.93, 128.29, 128.67, 130.52, 130.84, 133.79, 134.66, 144.76, 146.81, 149.32, 160.08, 162.83 ppm. ESI–MS (*m/z*): 475 $(M+1)^+$. Anal. Calcd for $C_{27}H_{18}N_6O_3$: C, 68.35; H, 3.82; N, 17.71. Found: C, 68.48; H, 3.91; N, 17.63.

General procedure for the synthesis of fused naphthopyrano[3,2-*e*]tetrazolo[2,3-*c*][1, 4]diazepines (5a–f)

A mixture of compound **2a–f** (2 mmol), 4-methoxyphenacyl bromide (2 mmol) and sodium acetate (2.4 mmol) in ethanol (10 mL) were refluxed for 24 h. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature then poured into water (20 mL) and then extracted with ethyl acetate (2 × 30 mL). The organic extract was separated, dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The residue was then purified by column chromatography on silica gel using hexane/ethyl acetate (6:4) as eluent to obtain compound **5a–f**.

15-Phenyl)-5-(4-methoxphenyl-15H-naphtho[1′,2′:5,6]pyrano[3,2-e][1–4]tetrazolo[2,3-c][1, 4]diazepine (5a)

Orange solid, yield: 56 %; mp: 216–218 °C. IR (KBr, cm^{-1}): 1,616, 1,591, 1,511, 1,402, 1,374, 1,219, 1,091. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.84 (s, 3H, OCH_3), 5.03 (s, 1H, pyran CH), 6.14 (s, 2H, CH_2), 7.11–7.17 (m, 4H, ArH), 7.27 (d, 2H, ArH), 7.57–7.89 (m, 8H, ArH), 8.26 (d, 1H, ArH) ppm. ^{13}C NMR (DMSO-d_6, 100 MHz): δ 40.98, 48.07, 55.14, 105.84, 118.77, 120.51, 120.72, 122.75, 123.82, 125.75, 126.28, 126.62, 126.72, 127.50, 127.64, 128.24, 129.21, 132.68, 133.37, 140.56, 142.71, 157.24, 159.23, 162.11, 164.05 ppm. ESI–MS (*m/z*): 472 $(M+1)^+$. Anal. Calcd for $C_{29}H_{21}N_5O_2$: C, 73.87; H, 4.49; N, 14.85. Found: C, 73.97; H, 4.37; N, 14.96.

15-(4-Chlorophenyl)-5-(4-methoxphenyl-15H-naphtho[1′,2′:5,6]pyrano[3,2-e][1–4]tetrazolo[2,3-c][1, 4]diazepine (5b)

Yellow solid, yield: 53 %; mp: 188–190 °C. IR (KBr, cm^{-1}): 1,610, 1,594, 1,517, 1,411, 1,372, 1,218, 1,088. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.86 (s, 3H, OCH_3), 5.08 (s, 1H, pyran CH), 6.18 (s, 2H, CH_2), 6.98–7.22 (m, 4H, ArH), 7.33–7.59 (m, 8H, ArH), 7.81 (d, 1H, ArH), 8.17 (d, 1H, ArH) ppm. ^{13}C NMR (DMSO-d_6,

100 MHz): δ 41.11, 48.23, 55.38, 105.67, 118.62, 120.61, 120.83, 123.42, 124.76, 125.81, 126.52, 126.71, 126.88, 127.73, 129.23, 129.43, 131.24, 133.32, 133.84, 142.86, 145.42, 157.31, 159.17, 162.29, 164.31 ppm. ESI–MS (*m/z*): 506 $(M+1)^+$. Anal. Calcd for $C_{29}H_{20}ClN_5O_2$: C, 68.84; H, 3.98; N, 13.84. Found: C, 68.76; H, 3.89; N, 13.92.

15-(4-Fluorohenyl)-5-(4-methoxphenyl-15H-naphtho[1′,2′:5,6]pyrano[3,2-e][1–4]tetrazolo[2,3-c][1,4]diazepine (5c)

Brown solid, yield: 55 %; mp: 170–172 °C. IR (KBr, cm^{-1}): 1,613, 1,594, 1,532, 1,414, 1,379, 1,228, 1,087. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.85 (s, 3H, OCH_3), 5.10 (s, 1H, pyran CH), 6.15 (s, 2H, CH_2), 7.02–7.23 (m, 4H, ArH), 7.31–7.60 (m, 8H, ArH), 7.84 (d, 1H, ArH), 8.19 (d, 1H, ArH) ppm. ^{13}C NMR (DMSO-d_6, 100 MHz): δ 41.17, 48.26, 55.47, 105.54, 118.47, 120.28, 120.74, 123.67, 124.71, 125.83, 126.14, 126.65, 126.79, 127.62, 129.24, 129.63, 131.41, 133.53, 133.71, 142.79, 145.38, 157.26, 159.21, 162.13, 164.09 ppm. ESI–MS (*m/z*): 490 $(M+1)^+$. Anal. Calcd for $C_{29}H_{20}FN_5O_2$: C, 71.16; H, 4.12; N, 14.31. Found: C, 71.27; H, 4.21; N, 14.23.

15-(4-Methylphenyl)-5-(4-methoxphenyl-15H-naphtho[1′,2′:5,6]pyrano[3,2-e][1–4]tetrazolo[2,3-c][1, 4]diazepine (5d)

Orange solid, yield: 50 %; mp: 176–178 °C. IR (KBr, cm^{-1}): 1,602, 1,596, 1,527, 1,434, 1,377, 1,216, 1,090. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.28 (s, 3H, CH_3), 3.87 (s, 3H, OCH_3), 5.12 (s, 1H, pyran CH), 6.22 (s, 2H, CH_2), 6.96–7.27 (m, 4H, ArH), 7.36–7.61 (m, 8H, ArH), 7.83 (d, 1H, ArH), 8.20 (d, 1H, ArH) ppm. ^{13}C NMR (DMSO-d_6, 100 MHz): δ 22.02, 41.24, 48.34, 55.57, 105.67, 118.37, 120.62, 123.38, 124.71, 125.83, 126.31, 126.68, 126.87, 127.24, 128.17, 128.43, 128.87, 130.29, 130.54, 133.67, 137.62, 142.14, 157.63, 159.34, 162.19, 164.23 ppm. ESI–MS (*m/z*): 486 $(M+1)^+$. Anal. Calcd for $C_{30}H_{23}N_5O_2$: C, 74.21; H, 4.77; N, 14.42. Found: C, 74.13; H, 4.69; N, 14.53.

5,15-Di-(4-Methoxyphenyl)-15H-naphtho[1′,2′:5,6]pyrano[3,2-e][1–4]tetrazolo[2,3-c][1, 4]diazepine (5e)

Brown solid, yield: 47 %; mp: 204–206 °C. IR (KBr, cm^{-1}): 1,610, 1,592, 1,536, 1,422, 1,377, 1,211, 1,087. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.85 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 5.17 (s, 1H, pyran CH), 6.24 (s, 2H, CH_2), 7.00–7.24 (m, 4H, ArH), 7.42–7.61 (m, 8H, ArH), 7.82 (d, 1H, ArH), 8.23 (d, 1H, ArH) ppm. ^{13}C NMR (DMSO-d_6, 100 MHz): δ 41.37, 49.17, 55.88, 55.94, 105.12, 114.90, 118.86, 120.11, 121.17, 123.58, 124.74, 126.18, 126.87, 127.34, 127.87, 128.39, 128.76, 129.53, 130.34, 133.72, 144.86, 157.32, 158.21, 159.73, 162.52, 164.47 ppm. ESI–MS (*m/z*): 502 $(M+1)^+$. Anal. Calcd for $C_{30}H_{23}N_5O_3$: C, 71.84; H, 4.62; N, 13.96. Found: C, 71.76; H, 4.71; N, 13.88.

15-(3-Nitrophenyl)-5-(4-methoxphenyl-15H-naphtho[1′,2′:5,6]pyrano[3,2-e][1–4]tetrazolo[2,3-c][1, 4]diazepine (5f)

Brown solid, yield: 43 %; mp: 241–244 °C. IR (KBr, cm^{-1}): 1,619, 1,590, 1,541, 1,422, 1,375, 1,218, 1,087. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.89 (s, 3H, OCH_3), 5.21 (s, 1H, pyran CH), 6.27 (s, 2H, CH_2), 7.04–7.47 (m, 8H, ArH), 7.53 (t, 1H, ArH), 7.59 (d, 1H, ArH), 7.84 (d, 1H, ArH), 8.06 (d, 1H, ArH), 8.16 (s, 1H, ArH), 8.27 (d, 1H, ArH), ppm. ^{13}C NMR (DMSO-d_6, 100 MHz): δ 41.42, 49.34, 55.96, 105.43, 118.26, 119.84, 121.37, 122.54, 123.45, 123.86, 125.47, 125.72, 126.39, 127.54, 127.76, 128.37, 130.43, 130.67, 133.70, 134.53, 144.85, 146.73, 149.32, 157.42, 159.21, 162.78, 164.69 ppm. ESI–MS (*m/z*): 517 $(M+1)^+$. Anal. Calcd for $C_{29}H_{20}N_6O_4$: C, 67.44; H, 3.90; N, 16.27. Found: C, 67.51; H, 3.98; N, 16.19.

Biological protocol

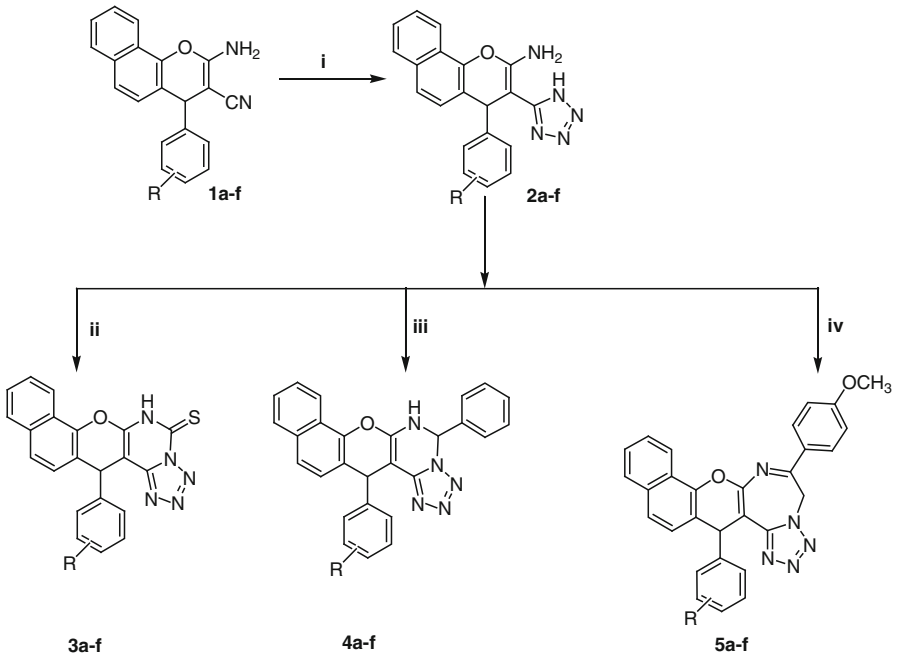
Antimicrobial activity

All the newly synthesized compounds **2a–f**, **3a–f**, **4a–f**, and **5a–f** were screened for their antibacterial activity against Gram-positive bacteria (*B. subtilis*, *S. aureus*) and Gram-negative bacteria (*P. aeuroginosa*, *E. coli*). The antifungal activity of the compounds was assayed against *C. albicans* and *A. niger*. The MICs of the compound assays were carried out using the microdilution susceptibility method. Ciprofloxacin was used as reference antibacterial agent. Fluconazole was used as reference antifungal agent. The test compounds, ciprofloxacin and fluconazole, were dissolved in DMSO at a concentration of 800 μg/mL, then diluted in culture medium (nutrient agar for bacteria and potato dextrose agar for fungi), and two-fold serial dilutions of the solution was prepared (400, 200, 100, 50, 25, 12.5 and 6.25 μg/mL). The tubes were incubated at 36 °C for 24 h and 48 h for bacteria and fungi, respectively. The minimum inhibitory concentrations (MIC, μg/mL) of the compounds were recorded as the lowest concentration of each chemical compounds in the tubes with no turbidity (i.e. no growth) of inoculated bacteria/fungi.

Results and discussion

The reaction sequences employed for the synthesis of compounds **2a–f**, **3a–f**, **4a–f**, and **5a–f** are shown in Scheme 1. The starting materials used in the present study, namely 2-amino-4-aryl-benzo[*h*]chromene-3-carbonitriles **1a–f**, were prepared by a known procedure [37]. The compound **1a–f** on reaction with sodium azide in presence of dimethylformamide gave corresponding tetrazole derivatives **2a–f**. The six- and seven-membered fused heterocycles **3a–f**, **4a–f**, and **5a–f** were prepared by cyclization of **2a–f** with carbon disulfide, benzaldehyde and 4-methoxyphenacyl bromide, respectively. The physical data of synthesized compounds are given in the "Experimental" section.

The structures of all the newly synthesized compounds were established on the basis of their spectral and elemental data. Spectral data of compounds were in full



R = (a) H, (b) 4-Cl, (c) 4-F, (d) 4-Me, (e) 4-OMe, (f) 3-NO_2

Scheme 1 Schematic representation for the synthesis of fused tetrazole derivatives. Reagent and conditions: (i) NaN_3, DMF, NH_4Cl, 120 °C, 7 h; (ii) CS_2, pyridine, reflux, 16 h; (iii) Conc. HCl, benzaldehyde, MeOH, reflux, 20 h; (iv) 4-Methoxyphenacyl bromide, MeOH, AcONa, reflux 24 h

agreement with proposed structures. The formation of tetrazolylbenzo[*h*]chromene **2a–f** from 2-amino-benzo[*h*]chromeno-3-carbonitrile **1a–f** was confirmed by its IR, NMR and mass spectral data. In IR spectra, the presence of a –NH band at 3,383–3,471 cm^{-1} and absence of a sharp absorption band (CN) around 2,200 cm^{-1} showed the formation of tetrazole, while ^{1}H NMR showed a singlet at δ 10.32–10.61 ppm due to the –NH proton. In ^{13}C NMR, the tetrazole carbon was observed at δ 161.20–161.96 ppm. Further, the cyclization of **2a–f** and **3a–f** was supported by its IR, NMR and mass spectra. In its IR spectrum, NH stretching vibrations appeared around 3,387–3,413 cm^{-1}, and a band near 1,167–1,181 cm^{-1} confirms the C=S group in the synthesized compounds. The ^{1}H NMR spectrum of **3a–f** exhibited a singlet at δ 10.32–10.52 ppm due to the proton of –NH. The formation of **3a–f** was further confirmed by its ^{13}C NMR, in which the signal due to C=S was observed around δ 189.51–190.14 ppm. Similarly, the formation of **4a–f** and **5a–f** were also confirmed by their IR, NMR, and mass spectral data. The ^{1}H NMR of **4a–f**, demonstrated a singlet at δ 5.81–6.13 ppm due to the –CH proton of the pyrimidine ring and its ^{13}C NMR showed a signal at δ 64.12–65.31 ppm. In the IR spectrum of **5a–f**, the disappearance of bands around 3,202–3,471 cm^{-1} due to $–NH_2$ and –NH groups clearly confirms the formation of fused tetrazolodiazepine ring. In its ^{1}H NMR and ^{13}C NMR, peaks due to the $–CH_2$ group were observed at δ 6.14–6.27 ppm and δ 48.07–49.34 ppm, respectively, which clearly indicate the smooth cyclization. In all

the synthesized compounds the pyran proton was observed in the range of δ 4.80–5.34 ppm and all other aromatic and aliphatic protons were observed at the expected regions. The mass spectra detected the expected molecular ion signals corresponding to respective molecular formula of the synthesized compounds. The elemental analyses values were in good agreement with the theoretical data. The detailed spectral data are given in the "Experimental" section..

Antimicrobial activity

The antibacterial activity of the synthesized compounds **2a–f**, **3a–f**, **4a–f**, and **5a–f** was screened against Gram-positive bacteria such as *Bacillus subtilis*,

Table 1 Minimum inhibitory concentration (MIC, μg/mL) of synthesized compounds **2a–f**, **3a–f**, **4a–f**, and **5a–f**

Compound	Gram +ve bacteria		Gram −ve bacteria		Fungi	
	B. subtilis	*S. aureus*	*P. aeuroginosa*	*E. coli*	*C. albicans*	A. *niger*
2a	400	–	–	–	400	400
2b	200	400	100	400	200	400
2c	200	100	200	100	50	50
2d	400	–	–	400	400	400
2e	200	100	200	100	200	100
2f	400	–	–	–	–	400
3a	200	400	400	400	400	200
3b	400	400	400	200	400	400
3c	200	200	200	400	400	200
3d	50	25	100	100	100	50
3e	400	200	200	200	200	400
3f	400	400	400	400	400	400
4a	400	200	400	400	200	400
4b	400	400	400	200	400	400
4c	400	200	400	400	400	400
4d	400	400	400	200	400	400
4e	50	100	100	50	25	50
4f	400	400	400	400	400	400
5a	–	–	–	400	–	–
5b	400	–	–	400	–	–
5c	400	400	–	–	–	–
5d	200	400	200	400	200	400
5e	400	200	200	400	400	200
5f	–	400	–	–	–	–
Ciprofloxacin	6.25	6.25	6.25	6.25		
Fluconazole					6.25	6.25

Staphylococcus aureus, and Gram-negative bacteria, i.e. *Pseudomonas aeruginosa*, *Escherichia coli*, using nutrient agar medium. The antifungal activity of the compounds was tested against *Candia albicans* and *Aspergillus niger* using potato dextrose agar medium. The minimum inhibitory concentration (MIC) was carried out using the microdilution susceptibility method [38]. Ciprofloxacin was used as a standard antibacterial drug and fluconazole was used as standard antifungal drug. The observed data on the antimicrobial activity of compounds and control drugs are given in Table 1.

The results of antimicrobial activity data of tested compounds revealed that, among the screened compounds, only compounds **3d** and **4e** were found to be active against *B. subtilis*. Compound **3d** displayed good activity towards *S. aureus*, whereas compound **4e** showed good activity against *E. coli*. The remaining compounds showed moderate to poor activity towards both bacteria.

Amongst the tested compounds, only compounds **2c** and **4e** were found to be potent against both fungal strains. Compound **3d** exhibited good activity towards *A. niger*. Except **2c**, **3d**, and **4e** , the remaining compounds showed moderate to poor activity against fungi. The structure–activity relationship of the synthesized compounds revealed that the compounds having a diazepine ring showed least activity compared to other compounds.

Conclusion

In conclusion, we have designed and synthesized a new series of fused naphthopyranotetrazolopyrimidines, thiopyrimidines, and diazepines. Various chemical and spectral data supported the structures of the newly synthesized compounds. The synthesized compounds were screened for their in vitro antibacterial and antifungal activity. Among the tested compounds, **3d** and **4e** displayed good activity against both bacterial and fungal strains, whereas compound **2c** exhibited good activity towards fungi.

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