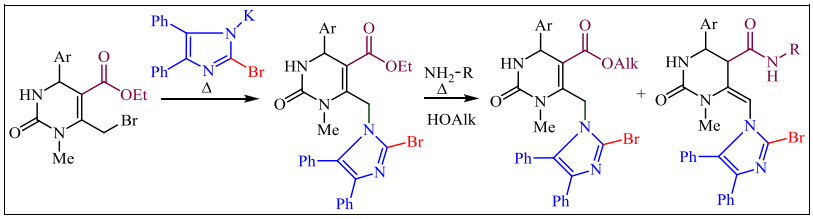
Functionalized Diphenyl-Imidazolo-Pyrimidines

Pavel P. Lyubashov,[a] Vyacheslav M. Povstyanoy,[a] Andrey A. Krysko,[b] Alexander Plotkin,[c] Ilene Lovett,[c] Mykhailo V. Povstyaniy,[a] and Iryna O. Lebedyeva[c]*

[a]Department of Chemical Technology and Food Safety, Kherson National Technical University, Berislavs'ke Highway 24, Kherson 73008, Ukraine
[b]Department of Medicinal Chemistry, A.V. Bogatsky Physico-Chemical Institute of the National Academy of Sciences of Ukraine, Lustdorfskaya St., 86, Odessa 65080, Ukraine
[c]Department of Chemistry and Physics, Augusta University, 1120 15th Street, Augusta, GA 30912, USA
*E-mail: ilebedyeva@augusta.edu

Received August 20, 2017
DOI 10.1002/jhet.3044
Published online 00 Month 2017 in Wiley Online Library (wileyonlinelibrary.com).



Synthesis of novel imidazopyrimidines has been reported. These systems contain carbethoxy group at C5 of pyrimidine and bromine at C2 of imidazole. Reactivity of these two groups was studied, and the mobility of the carbethoxy group was confirmed by tracing the formation of the amide product and also with isolation of alkyl analogs while bromine did not react with N-nucleophiles under various reaction conditions employed. New conjugates combine the properties of dihydropyrimidine and imidazole and therefore lead to the expansion of original properties of each heterocyclic moiety within the system.

J. Heterocyclic Chem., **00,** 00 (2017).

INTRODUCTION

Heterocycles have been known for providing important building blocks for natural bioactive compounds [1,2] and pharmaceuticals [3,4]. Dihydropyrimidines (DHPMs), synthesized via Biginelli reaction, proved to be useful for both anticancer, for example, Monastrol (**1**; Fig. 1) [3,5] and antihypertensive agents, for example, SQ 32547 (**2**; Fig. 1) [6,7]. Monastrol **1** [3,8–10], the inhibitor of mitotic kinesin Eg5 [10], is one of several successful examples when DHPMs reached pharmaceutical market. There are also a number of drug candidates that exhibit calcium channel modulation [11], inhibition of kinases and G protein–coupled receptors [12], and DNA intercalation [13] types of activities that are currently being studied on in vitro and in vivo models. Besides providing pyrimidines as small molecules for compound libraries, the three-component Biginelli reaction has proven to be a convenient gateway to complex constructs of natural alkaloids such as crambescidin 800 (**3**; Fig. 1) [1], *Monanchora arbuscula*, *Clathria calla* [14], (+)-ptilomycalin A [15], batzelladine F [16], and analogs [17].

Heterocycles are represented with many families of bioactive compounds, and to explore the possibility of enhancement of biological properties for pyrimidines, we considered creating a combination of DHPMs with diphenylsubstituted imidazoles. Imidazoles [18] have been historically known for their antifungal [19] and antibacterial properties [20]. Substituted imidazoles have been presented on pharmaceutical market with ketocanazole **4** [21], metronidazole **5** [22], miconazole **6** [23], and clotrimazole **7** [24] (Fig. 2). In addition, imidazole is a part of histidine, a common building block of proteins [25], bioactive peptides [26], and natural alkaloids [27,28].

Combination of pyrimidines and imidazoles with the possibility of their further functionalization is of considerable practical interest because of the novelty of this approach and the therapeutic potential of the new bisheterosystems. Our group has previously worked with creating bisconjugates through combination of DHPMs with theophylline [29]. This approach led to formation of intermediates with two reactive centers. Difunctionalized intermediates formed several products that included ring closure and pyrimidine ring restructuring under conditions of high pressure and temperatures in presence of N-nucleophiles. Our previous work on creation of bisheterocycles [29] has been summarized in Scheme 1.

In this work, the reaction of the potassium salt 2-bromo-4,5-diphenyl-1*H*-imidazole **15** with 2-oxo-4-aryl-5-ethoxycarbonyl-6-bromomethylpyrimidines **16** along with further reaction ability of the newly formed imidazopyrimidines has been investigated. It is anticipated that the combination of substituted imidazoles and DHPMs will lead to an increase and diversification of the biological activity of novel conjugates.

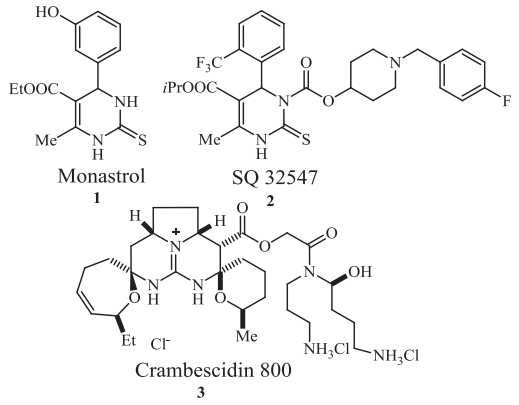


Figure 1. Bioactive DHPMs, products of Biginelli reaction.

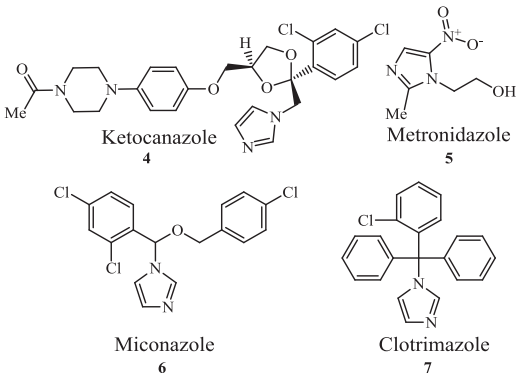


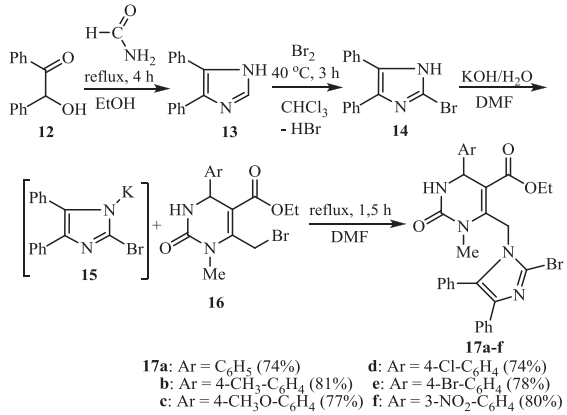
Figure 2. Imidazole-based drugs.

RESULTS AND DISCUSSION

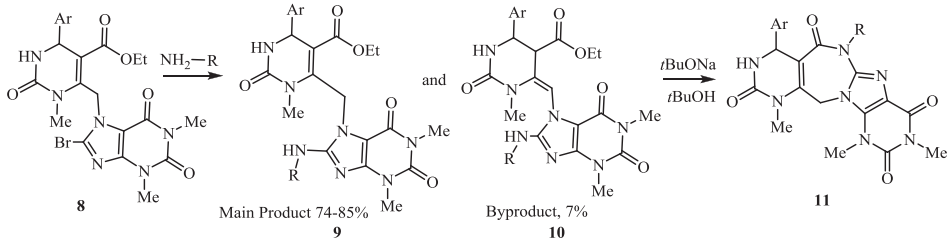
DHPMs **16** are reactive compounds functionalized in the 5-carbethoxy and 6-bromomethyl positions. Close proximity of two reactive centers in the pyrimidine ring facilitates reactions of cyclization with ethanol as a leaving group forming 5-, 6-, and 7-membered ring systems [29,30]. 4,5-Diphenylimidazole was constructed by condensation of benzoin **12** with formamide to form **13**. Diphenylimidazole **13** was then brominated at C2 to give **14**, which after the addition of KOH formed potassium salt **15** in situ. Product **17** (Scheme 2) was synthesized in 74–81% yields by coupling DHPM **16** and potassium 2-bromo-4,5-diphenyl-1*H*-imidazole in DMF under reflux. Precipitated products **17a**–**f** are bisheterocycles that contain carbethoxy group and the bromine atom.

A number of aliphatic and substituted benzyl amines were then used to explore possibilities for the substitution of carbethoxy and bromine groups of **17** to take place followed by subsequent cyclization. The aim was to react **17a** with a number of N-nucleophiles (Scheme 3) to explore whether the bromine atom at imidazole moiety would be substituted with the amino group with the possibility of the following step of the 7-membered ring cyclization of a product into a substituted 1*H*-imidazo[1,2-*a*]pyrimido[5,4-*e*][1,3]diazepine-2,5(3*H*,6*H*)-dione since our previous studies confirmed the possibility of formation of such products [29]. To facilitate the reaction, the following reaction conditions were used: (i) heating of **17a** and N-nucleophiles at DMF for 6 h and (ii) heating of reagents in alcohol in the high-pressure tube for 12 h. In this work, the formation of the product **19** was detected at 24.7% (Fig. S4). The product with the molecular mass of 588.0 [M + 1] was detected by the

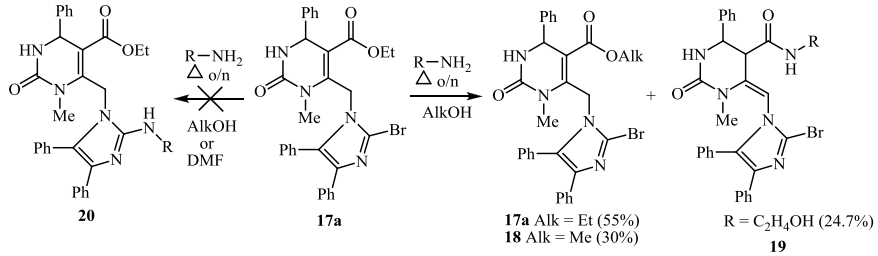
Scheme 2. Synthesis of pyrimidoimidazoles **17a**–**f**.



Scheme 1. Synthesis of 1,3-diazepinopyrinopyrimidines **11**.



Scheme 3. Synthesis of products **18** and **19**.



LC/MS after the 12-h reaction of **17a** with monoethanolamine in EtOH in a sealed tube. The structure of similar amide products was previously confirmed via X-ray analysis [29]. Reorganization of the ester moiety up to 30% also took place when the reaction with N-nucleophiles was conducted for 12 h in a sealed tube using MeOH as the solvent. Structure of the product **18** was confirmed with X-ray analysis (Fig. 4). Overall, the ester group of **17** has been more prone to structural modifications much easier than the bromine atom at the imidazole ring of **17** even under harsh reaction conditions. The fact that imidazole is substituted with two phenyl groups and can sterically hinder interactions with the nucleophiles may partially explain the unexpectedly low reactivity of the halogen atom at the imidazole ring. Structure of **17a** has been confirmed with X-ray analysis (Fig. 3).

^{1}H NMR spectra for compounds of type **17a**–**f** revealed signals of the ethyl group of DHPM moiety as a triplet at around 1.14–1.16 ppm and a quartet of a CH_2 group at around 5.13–5.20 ppm. The NMe group was detected at around 2.68–2.71 as a singlet. CH_2 group of DHPM at C6 was identified with two doublet peaks: a broad singlet or a multiplet signal at around 3.96–4.04 ppm. CH group of DHPM was presented either with a doublet or with a broad singlet at around 5.13–5.20 ppm. The signal of an NH group was identified at around 7.69–7.87 ppm. Signals of the aromatic moiety of DHPM as well as the signals for diphenylimidazole part of the molecule were visible at the aromatic area between 6.43 and 7.89 ppm. Additional signals of Me group for **17b** and OMe group for **17c** were observed as singlets at 2.21 and 3.69 ppm correspondingly (Fig. 4).

^{13}C signals for compounds **17a**–**f** were identified with the signals of the ethyl group of DHPM between 14.4 ppm for CH_3 and 60.6–60.8 ppm for CH_2. NMe group gave a signal at around 31.0–31.2 ppm. CH of DHPM was observed at around 52.1–52.3 ppm. NH–C=O group of DHPM was observed at 145.3–146.2 ppm, and the carbon peak for the CO group of the ester part of DHPM was observed between 153.3 and 153.6 ppm. Two quaternary carbons of the –C=C– moiety were observed at 138.1 ppm and between 106.4 and 108.0 ppm correspondingly. Signals of aromatic carbons for both DHPM and diphenylimidazole were observed at the aromatic area between 121.0 and 140.4 ppm. Imidazole moiety was also characterized with the peak for the C–Br at around 121.2–121.7 ppm and two signals for quaternary carbons at 133 and 127 ppm. Signals for the 4-Me-Ar for **17b** and 4-OMe-Ar of **17c** were identified at 21.1 and 55.5 ppm respectfully.

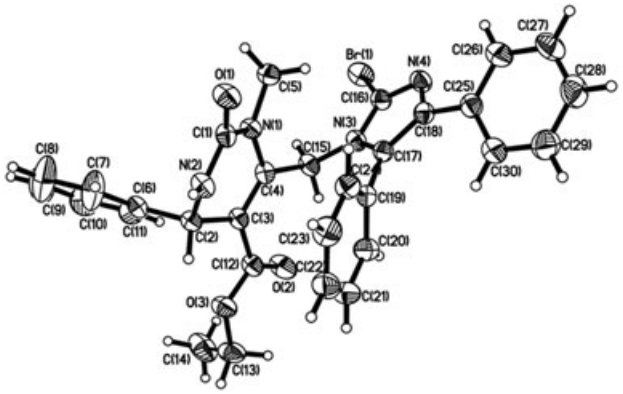


Figure 3. Molecular structure of **17** according to the X-ray analysis.

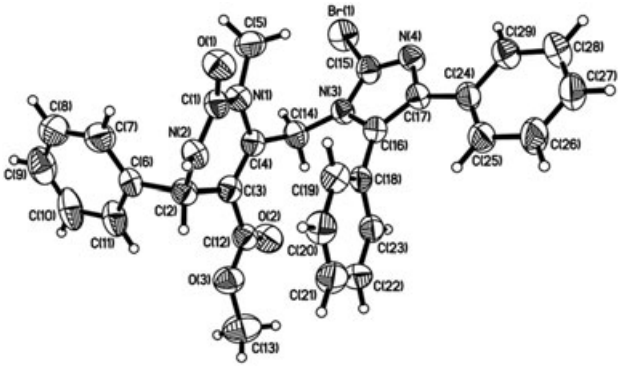


Figure 4. Molecular structure of **18** according to X-ray analysis.

The DHPM core acquired boat conformation and the N(1) and C(2) atoms formed the 0.24(1) and 0.46(1) Å angles with other atoms within the pyrimidine core. The precision of measurements was 0.03 Å, and the parameters of the DHPM core were S = 0.54, θ = 71.6°, ψ = 12.5°, which is common for compounds with similar structure [31] (see Supplementary Information for more details).

Analysis of the X-ray data for **18** revealed that the DHPM cycle acquires boat conformation with the deviation of N(1) и C(2) atoms from the other atoms in the ring on 0.26(2) and 0.44(2) Å, correspondingly (the precision of measurements is 0.02 Å, the parameters of the cycle are S = 0.53, θ = 75.0°, ψ = 9.4°), which corresponds with the parameters for the cycles of this type [31] (see Supporting Information for more details).

CONCLUSION

A method towards functionalized pyrimidoimidazoles has been developed. With this approach, two biologically active systems have been combined to synthesize a library of substituted pyrimidoimidazole heterosystems **17a**–**f** in high yields. Further on, the reactivity of these systems has been tested. It has been identified that the 2-bromo 4,5-diphenylimidazole part of the heterosystem was not as highly reactive as the halogens at C8 of the previously reported theophylline analogs [29]. Carbethoxy group participated in the alkyl group rearrangement and also some nucleophile substitution depending on the reaction conditions. This work will be translated further on multifunctional heterocycles to investigate the reactivity and also the biological activity potential of the polycyclic heterosystems, which contain pyrimidine fragment.

EXPERIMENTAL

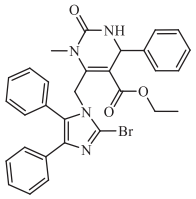
^{1}H NMR spectra were recorded at 400 MHz, and ^{13}C NMR spectra were recorded at 100 MHz at room temperature using either $CDCl_3$ or DMSO-d_6 as solvents. Chemical shifts are reported in ppm relative either to TMS as internal standard or to the residual solvent peak. The following abbreviations are used to describe spin multiplicity: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), brs (broad singlet), and dd (doublet of doublets). The LC/MS was recorded on Agilent 1100 with LC/MSD SLMobile Phase: A-H_2O + 0.1%HCOOH; B-MeCN + 0.1HCOOH. Elemental analysis was performed on PerkinElmer analyzer 2400 CHNS/O Series II System (100 V). X-ray diffraction analysis of single crystals of **17** (CCDC 1572960) and **18** (CCDC 1572959) was performed with an "Xcalibur 3" diffractometer (graphite-monochromated Mo-Kα radiation, λ = 0.71073) at 100 K.

Synthesis of 4,5-diphenyl-1*H*-imidazole 13. Benzoin (212 g, 1.0 mol) was dissolved in 350 mL of ethanol, and the excess of formamide was added to the solution. The mixture was then kept under reflux for 4 h. After the reaction mixture cooled to the room temperature, the precipitate was filtered off and washed with MeOH. Product **13** was recrystallized from DMF and isolated as white solid in 95% (209 g).

Synthesis of 2-bromo-4,5-diphenyl-1*H*-imidazole 14. 4,5-Diphenyl-1*H*-imidazole **13** (22 g, 0.1 mol) was suspended in chloroform (250 mL). The mixture was then heated up to 40°C, and Br_2 (8.5 mL) was slowly added dropwise. In 1.5 h, the color of the reaction mixture turned dark red. The reaction mixture was stirred for additional 1.5 h at 40°C. After that the reaction mixture was taken to dryness under vacuum. Product **14** was purified by recrystallization from *i*-PrOH/H2O 9/1 and isolated as yellow solid in 60% yield (17.9 g).

Synthesis of 2-bromo-4,5-diphenylimidazolopyrimidines 17. To the solution of 2-bromo-4,5-diphenyl-1*H*-imidazole **14** (2.99 g, 0.01 mol) in DMF (10 mL), KOH (0.56 g, 0.01 mol) was added in H_2O (2 mL) at room temperature, and the mixture was then stirred for 3 h. Correspondingly, 6-bromomethyl DHPM **16** was then added to the mixture that contained potassium 2-bromo-4,5-diphenyl-1*H*-imidazole **15** formed in situ and the mixture was kept under reflux for 60–90 min. After the reaction mixture cooled to room temperature, it was poured into cold deionized water (100 mL), and the precipitated product **17** was filtered off and washed with cold MeOH. Product **17** was purified with recrystallization from *i*-PrOH/H_2O 9/1 and isolated as white solid with the yields of 74–81%.

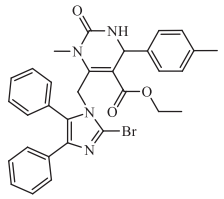
Ethyl 6-((2-bromo-4,5-diphenyl-1H-imidazol-1-yl)methyl)-1-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (17a).



White solid, yield 74%, mp 180°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.15 (t, *J* = 7.1 Hz, 3 H), 2.71 (s, 3 H), 3.99–4.04 (m, 2 H), 4.74 (brs, 1 H), 5.16 (d, *J* = 17.1 Hz, 1 H), 6.42 (d, *J* = 17.1 Hz, 1 H), 7.10–7.12 (d, *J* = 8.0 Hz, 2 H), 7.16–7.14 (d, *J* = 8.0 Hz, 1 H), 7.17–7.22 (m, 3 H), 7.25–7.28 (m, 4 H), 7.33 (d,

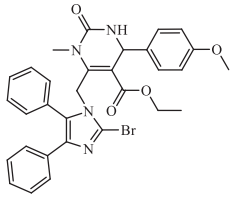
J = 7.3 Hz, 2 H), 7.42 (t, *J* = 7.6 Hz, 2 H), 7.50 (t, *J* = 7.3 Hz, 1 H), 7.78 (s, 1 H); ^{13}C (100 MHz, DMSO-d_6): δ = 164.8, 153.6, 145.7, 143.4, 138.1, 133.9, 131.4, 130.8, 129.8, 129.8, 129.3, 129.0, 128.7, 127.9, 127.2, 126.6, 126.3, 121.7, 107.7, 60.6, 52.1, 44.0, 31.1, 14.4. *Anal*. Calcd for $C_{30}H_{27}BrN_4O_3$: C, 63.05; H, 4.76; N, 9.80. Found: C, 63.41; H, 4.42; N, 9.91.

Ethyl 6-((2-bromo-4,5-diphenyl-1H-imidazol-1-yl)methyl)-1-methyl-2-oxo-4-(p-tolyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (17b).



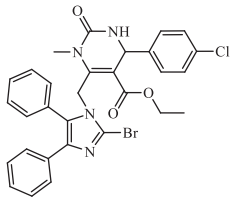
White solid, yield 81%, mp 220–223°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.16 (t, *J* = 7.1 Hz, 3 H), 2.23 (s, 3 H), 2.71 (s, 3 H), 4.01 (brs, 2 H), 4.72 (s, 1 H), 5.13 (d, *J* = 12.0 Hz, 2 H), 6.40 (d, *J* = 12.0 Hz, 1 H), 7.00 (d, *J* = 8.0 Hz, 2 H), 7.06 (d, *J* = 8.0 Hz, 2 H), 7.14–7.21 (m, *J* = 6.8 Hz, 2 H), 7.26 (d, *J* = 4.0 Hz, 2 H), 7.33 (d, *J* = 4.0 Hz, 2 H), 7.42 (t, *J* = 5.4 Hz, 2 H), 7.49 (d, *J* = 6.3 Hz, 1 H), 7.69 (s, 1 H); ^{13}C (100 MHz, DMSO-d_6): δ = 164.9, 153.6, 145.5, 140.4, 138.1, 137.1, 133.9, 131.4, 130.8, 129.8, 129.7, 129.5, 129.3, 128.7, 126.5, 126.3, 121.7, 107.8, 60.6, 52.3, 44.0, 31.1, 21.1, 14.4. *Anal*. Calcd for $C_{31}H_{29}BrN_4O_3$: C, 63.59; H, 4.99; N, 9.57. Found: C, 63.24; H, 4.76; N, 9.32.

Ethyl 6-((2-bromo-4,5-diphenyl-1H-imidazol-1-yl)methyl)-4-(4-methoxyphenyl)-1-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (17c).



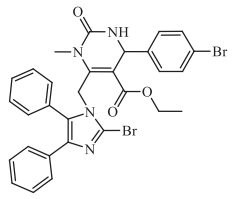
White solid, yield 77%, mp 223–224°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.15 (t, *J* = 7.1 Hz, 3 H), 2.69 (s, 3 H), 3.69 (s, 3 H), 3.99 (m, 2 H), 4.67 (d, *J* = 3.4 Hz, 1 H), 5.15 (d, *J* = 17.1 Hz, 1 H), 6.43 (d, *J* = 17.1 Hz, 1 H), 6.81 (d, *J* = 8.8 Hz, 2 H), 7.00 (d, *J* = 8.8 Hz, 2 H), 7.12–7.18 (m, 3 H), 7.25 (d, *J* = 7.3 Hz, 2 H), 7.33 (d, *J* = 4.0 Hz, 2 H), 7.41 (t, *J* = 7.6 Hz, 2 H), 7.49 (t, *J* = 7.1 Hz, 1 H), 7.75 (brs, 1 H); ^{13}C (100 MHz, $CDCl_3$): δ = 164.8, 159.0, 153.5, 145.3, 138.1, 135.5, 133.8, 131.4, 130.8, 129.8, 129.7, 129.3, 128.6, 127.8, 127.2, 126.2, 121.6, 114.2, 108.0, 60.5, 55.5, 52.1, 44.0, 31.0, 14.4. *Anal*. Calcd for $C_{31}H_{29}BrN_4O_4$: C, 61.90; H, 4.86; N, 9.31. Found: C, 61.74; H, 4.56; N, 9.48.

Ethyl 6-((2-bromo-4,5-diphenyl-1H-imidazol-1-yl)methyl)-4-(4-chlorophenyl)-1-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (17d).



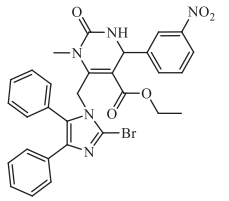
White solid, yield 74%, mp 193–195°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.14 (t, *J* = 7.1 Hz, 3 H), 2.68 (s, 3 H), 3.96–4.03 (m, 2 H), 4.70 (d, *J* = 4.4 Hz, 1 H), 5.18 (d, *J* = 17.1 Hz, 1 H), 6.44 (d, *J* = 17.1 Hz, 1 H), 7.12–7.14 (d, *J* = 8.0 Hz, 2 H), 7.16–7.21 (m, 3 H), 7.25 (d, *J* = 4.0 Hz, 2 H), 7.34–7.31 (m, 4 H), 7.41 (t, *J* = 7.6 Hz, 2 H), 7.49 (t, *J* = 7.3 Hz, 1 H), 7.87 (d, *J* = 3.9 Hz, 1 H); ^{13}C (100 MHz, DMSO-d_6): δ = 164.7, 153.4, 146.2, 142.3, 138.1, 133.8, 132.5, 131.2, 130.9, 129.8, 129.7, 129.3, 128.9, 128.7, 128.6, 127.2, 126.3, 121.7, 107.0, 60.7, 52.1, 44.0, 31.1, 14.4. *Anal*. Calcd for $C_{30}H_{26}BrClN_4O_3$: C, 59.47; H, 4.33; N, 9.25. Found: C, 59.85; H, 4.12; N, 9.47.

Ethyl 6-((2-bromo-4,5-diphenyl-1H-imidazol-1-yl)methyl)-4-(4-bromophenyl)-1-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (17e).



White solid, yield 78%, mp 205–207°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.15 (t, *J* = 7.1 Hz, 3 H), 2.69 (s, 3 H), 4.01 (q, *J* = 6.8 Hz, 2 H), 4.72 (brs, 1 H), 5.15 (d, *J* = 17.1 Hz, 1 H), 6.43 (d, *J* = 17.1 Hz, 1 H), 7.08 (d, *J* = 8.3 Hz, 2 H), 7.13–7.21 (m, 3 H), 7.25 (d, *J* = 7.3 Hz, 2 H), 7.33 (d, *J* = 7.3 Hz, 2 H), 7.39–7.51 (m, 5 H), 7.81 (s, 1 H); ^{13}C (100 MHz, $CDCl_3$): δ = 164.6, 153.4, 146.2, 142.7, 138.1, 133.8, 131.8, 131.3, 130.9, 129.8, 129.7, 129.3, 128.9, 129.6, 127.2, 126.3, 121.2, 121.1, 107.0, 60.7, 52.1, 44.0, 31.1, 14.4. *Anal*. Calcd for $C_{30}H_{26}Br_2N_4O_3$: C, 55.40; H, 4.03; N, 8.61. Found: C, 55.12; H, 4.00; N, 8.72.

Ethyl 6-((2-bromo-4,5-diphenyl-1H-imidazol-1-yl)methyl)-1-methyl-4-(3-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (17f).



White solid, yield 80%, mp 204–206°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.16 (t, *J* = 7.1 Hz, 3 H), 2.69 (s, 3 H), 4.04 (q, *J* = 7.2 Hz, 2 H), 4.85 (d, *J* = 3.9 Hz, 1 H), 5.20 (d, *J* = 17.1 Hz, 1 H), 6.48 (d, *J* = 17.1 Hz, 1 H), 7.13–7.21 (m, 3 H), 7.25 (d, *J* = 6.3 Hz, 2 H), 7.32 (d, *J* = 7.8 Hz, 2 H), 7.42 (t, *J* = 7.6 Hz, 2 H), 7.50 (t, *J* = 7.3 Hz, 1 H), 7.58 (d, *J* = 4.9 Hz, 2 H), 7.94 (s, 1 H), 8.01 (d, *J* = 3.9 Hz, 1 H), 8.08–8.11 (m, 1 H); ^{13}C (100 MHz, DMSO-d_6): δ = 164.5, 153.3, 148.3, 147.0, 145.5, 138.1, 133.8, 133.1, 131.3, 130.9, 130.8, 129.9, 129.7, 129.3, 128.7, 127.2, 126.3, 123.0, 121.7, 121.4, 106.4, 60.8, 52.1, 44.0, 31.2, 14.4. *Anal*. Calcd for $C_{30}H_{26}BrN_5O_5$: C, 58.45; H, 4.25; N, 11.36. Found: C, 58.29; H, 4.36; N, 11.68.

REFERENCES AND NOTES

[1] Aron, Z. D.; Overman, L. E. Chem Commun 2004, 253.

[2] Franklin, A. S.; Ly, S. K.; Mackin, G. H.; Overman, L. E.; Shaka, A. J Org Chem 1991, 64, 1512.

[3] Figueiro, F.; Mendes, F. B.; Corbelini, P. F.; Janarelli, F.; Jandrey, E. H. F.; Russowsky, D.; Eifler-Lima, V. L.; Battastini, A. M. O. Anticancer Res 2004, 34, 1837.

[4] Johnson, S.; Louie, T. J.; Gerding, D. N.; Cornely, O. A.; Chasan-Taber, S.; Fitts, D.; Gelone, S. P.; Broom, C.; Davidson, D. M. Clin Infect Dis 2014, 59, 345.

[5] Kumar, B. P.; Sankar, G.; Baig, R. N.; Chandrashekaran, S. Eur J Med Chem 2009, 44, 4192.

[6] Grover, G. J.; Dzwonczyk, S.; McMullen, D. M.; Normandin, D. E.; Parham, C. S.; Sleph, P. G. J Cardiovasc Pharmacol 1995, 26, 289.

[7] Kolosov, M. A.; Orlov, V. D.; Beloborodov, D. A.; Dotsenko, V. V. Mol Divers 2009, 13, 5.

[8] Kapoor, T. M.; Mayer, T. U.; Coughlin, M. L. J Cell Biol 2000, 150, 975.

[9] Maliga, Z.; Kapoor, T. M.; Mitchison, T. J Chem Biol 2002, 9, 989.

[10] Cochran, J. C.; Gatial, J. E.; Kapoor, T. M.; Gilbert, S. P. J Biol Chem 2005, 280, 12658.

[11] Kappe, C. O. Molecules 1998, 3, 1.

[12] Schneider, P.; Stutz, K.; Kasper, L.; Haller, S.; Reutlinger, M.; Reisen, F.; Geppert, T.; Schneider, G. Pharmaceuticals 2011, 4, 1236.

[13] Lebedyeva, I. A.; Povstyanoy, M. V.; Zubatyuk, R. I.; Shishkin, O. V.; Ihmels, H. Acta Crystallogr Sect E 2010, 66, o1762.

[14] Laville, R. M.; Thomas, O. P.; Berrué, F.; Marquez, D.; Vacelet, J.; Amade, P. J Nat Prod 2009, 72, 1589.

[15] Overman, L. E.; Rabinowitz, M. H. J Org Chem 1993, 58, 3235.

[16] Cohen, F.; Overman, L. E. J Am Chem Soc 2001, 123, 10782.

[17] Cohen, F.; Collins, S. K.; Overman, L. E. Org Lett 2003, 5, 4485.

[18] Zhang, L.; Peng, X. M.; Damu, G. L.; Geng, R. X.; Zhou, C. H. Med Res Rev 2014, 34, 340.

[19] Rittenhouse, A.; Vandorpe, D.; Brugnara, C.; Alper, S. J Membr Biol 1997, 157, 177.

[20] Sutherland, L.; Singleton, J.; Sessions, J.; Hanauer, S.; Krawitt, E.; Rankin, G.; Summers, R.; Mekhjian, H.; Greenberger, N.; Kelly, M. Gut 1991, 32, 1071.

[21] Sonino, N. N Engl J Med 1987, 317, 812.

[22] Löfmark, S.; Edlund, C.; Nord, C. E. Clin Infect Dis 2010, 50, S16.

[23] Van Cutsem, J.; Thienpont, D. Chemotherapy 1972, 17, 392.

[24] Robey, R. W.; McDonald, A. J.; Kozlowski, H.; Gottesman, M. M.; Bates, S. E. Am Assoc Cancer Res 2017. https://doi.org/10.1158/1538-7445.AM2017-4040.

[25] Cheng, Q.; Gatton, M. L.; Barnwell, J.; Chiodini, P.; McCarthy, J.; Bell, D.; Cunningham, J. Malar J 2014, 13, 283.

[26] Colzani, M.; Garzon, D.; Aldini, G. Imidazole Dipeptides 2015, 3, 139.

[27] Jin, Z. Nat Prod Rep 2016, 33, 1268.

[28] Shi, Q.; Hui, S.; Zhang, A.-H.; Hong-Ying, X.; Guang-Li, Y.; Ying, H.; Xi-Jun, W. Chin J Nat Med 2004, 12, 401.

[29] Lebedyeva, I. O.; Ryabitskii, A. B.; Panasyuk, O.; Ivahnenko, E.; Lozova, V. P.; Markevich, I.; Allakhverdova, S.; Povstyanoy, M. V. Eur J Org Chem 2013, 2013, 4594.

[30] Kappe, C. O. Tetrahedron 1993, 49, 6937.

[31] Groom, C. R.; Allen, F. H. Angew Chem Int Ed 2014, 53, 662.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.