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Synthesis, characterization, and antimicrobial evaluation of some novel Imidazo[1,2-*c*] pyrimidine derivatives

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ABSTRACT **: Due to chalcone compounds' diverse and intriguing bioactive characteristics, the present work recommends the production of several new chalcone derivatives, followed by spectral characterization utilizing various spectral techniques such as IR, NMR, and elemental analyses. In addition to, assessment the antimicrobial activity of imidazo[1,2-*c*] pyrimidine derivatives. All tested new chalcone compounds showed antibacterial activity against P. aeruginosa and B. subtilis, while only compounds (5a-d and 5f) displayed activity against E. coli. Furthermore, only compounds (5a-c, 5e and 5f) reduced the development of S. aureus. The compound 5f revealed significant antibacterial activity against S. aureus (87.5%), B. subtilis (82.61 %), P. aeruginosa (78.26%) and E. coli (64%), when compared to Ampicillin. On the other hand, the compounds (5a-d, 5e and 5f) showed antifungal activity against C. Albicans. Also, compounds (5a, 5b, 5c, 5d and 5f) displayed activity against A. flavus. A significant antifungal activity for compound 5b has been observed against C. Albicans (70.37%) and A. flavus (52%), when compared to Colitrima-zole.**

KEYWORDS: new chalcones, imidazo[1,2-c] pyrimidine, antibacterial activity, antifungal activity

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I. INTRODUCTION

Microbial infections, particularly bacterial infections, have become more widespread in recent decades, causing a high risk of mortality among immunocompromised people. Opportunistic bacterial infections represent a considerable risk to these people and are occurring at an alarming pace [1, 2]. Since there have been several reports on the isolation of bacteria that are known to be sensitive to commonly used antibiotics and have become multiresistant to other treatments on the market [3, 4].

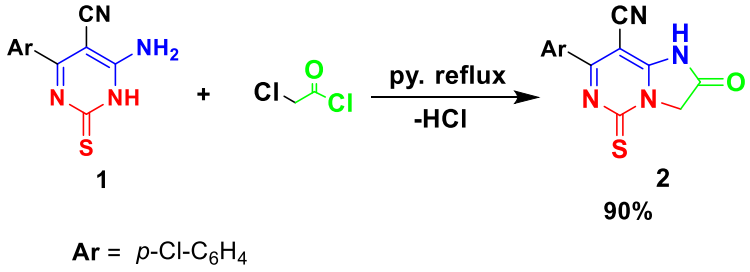
Undoubtedly, heterocyclic molecules, especially those with nitrogen atom, have important biological functions [5, 6]. Imidazopyrimidine scaffolds are important building blocks in drug design and development. Imidazopyrimidines, for example, have a diverse pharmacological profile, including anticancer [7], antitubercular [8], antiviral [9], antimicrobial [10], antifungal [11], anti-inflammatory [12], parasiticidal activity [13], calcium channel blockers [14], benzodiazepine receptor agonists [15], potent P38 MAP kinase inhibitors [16] and GABA receptor ligands [17]. It has also been used as an azodye [18], fabric whitener, insecticidal, acaricidal, and nematocidal agent [19]. It was also discovered to be a significant structural component of Divaplon [20] and Fasiplon [15] as a possible anxiolytic and anticonvulsant medication whose use in clinical practise was discontinued [21]. To expand its uses, this scaffold can also be employed as an organic flurophore in biomarkers and photochemical sensors [22].

In agreement with our previous interest in the synthesis of imidazopyrimidine derivatives [23-25], and because of the resulting pharmacological interest in compounds that belong to these heterocyclic derivatives, we would like to report a method for preparing some novel Imidazo[1,2-*c*] pyrimidine derivatives, as well as, an evaluation of their antimicrobial activity.

II. RESULTS AND DISCUSSION

Chemistry:

The current investigation began with the synthesis and characterization of 2-thioxo cytosine **1** which was then cyclized with chloroacetyl chloride to yield the imidazo[1,2-*c*] pyrimidine **2** as described in the literature **[24]** (Scheme 1). Compound **2** has *α*-CH acid function at *C*-3 and operates as an active site for the formation of new bioactive chemicals *via* Kneovenagel condensation.



Scheme 1: Synthesis of Imidazo[1,2-*c*] pyrimidine 2.

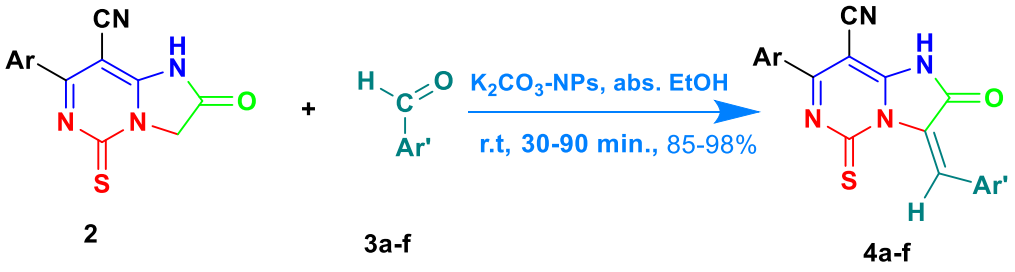
Condensation with an aromatic or hetero aromatic aldehyde in ethanol at room temperature for 30-90 minutes in the presence of K_2CO_3-NPs functionalizes C-H (sp3) at the third position in imidazo[1,2-*c*]pyrimidine 3 to benzylidene function. (Scheme 2). A variety of aromatic aldehydes were utilised (Table 1), including 4-hydroxybenzaldehyde, 2-methoxybenzaldehyde, 2-tolualdehyde, 3-nitrobenzaldehyde, 4-cyanobenzaldehyde, and 3-hydroxy-4-methoxybenzaldehyde. High yield (up to 96%) and short reaction time with aldehyde-containing electron withdrawing groups (e.g., CN, NO_2) (30 min.) were found. The aldehyde-containing electron-donating group (e.g., OH, OCH_3, CH_3), on the other hand, yields a high yield (87-98%).

The IR spectra of the synthesized compounds **4a-f** include four main bands in the ranges 3185-3371, 2190-2194, 1656-1697, and 1211-1317 cm^{-1} for the N-H, C≡N, C=O, and C=S functions, respectively.

The presence of a benzylidene proton as a singlet in the range δ_H = 4.61-6.79 ppm and the absence of a CH_2-imidazole ring in the ^{1}H-NMR spectrum of compounds **4a-f** are the main evidence promoting the condensation reaction and the synthesis of the target molecules. In addition, the aromatic component of aldehyde appeared in the expected field, and their ^{13}C-NMR corresponded to the chemical structure.

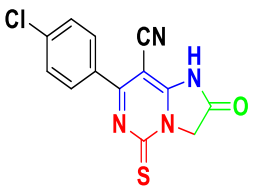
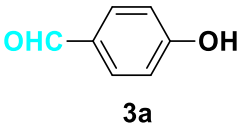
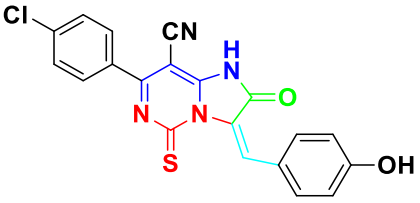
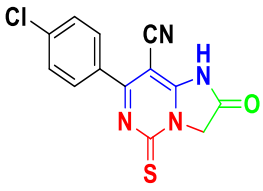
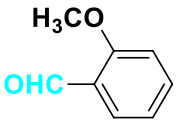
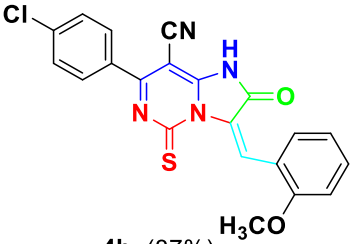
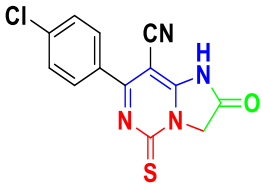
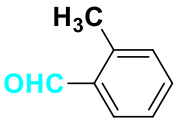
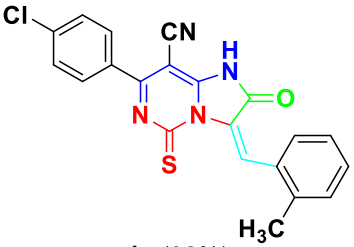
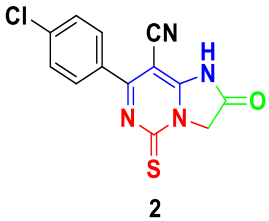
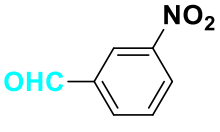
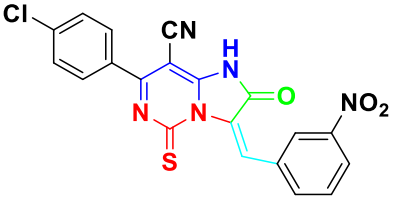
The ^{1}H-NMR chart of imidazopyrimidine **4a** assigned three singlets at δ_H 6.79, 10.49 and 11.51 ppm for benzylidene (=CH), OH and NH protons, respectively. Furthermore, at δ_H 7.22, 7.44, 7.63 and 7.71 ppm, the two aryl rings split into four doublets. Its ^{13}C-NMR chart recorded 16 signals for sp^3, sp^2, and sp carbons at δ_c 52.45, 113.9, 114.9, 118.3, 118.5, 126.0, 126.8, 127.3, 134.3, 135.8, 142.8, 152.4, 158.2, 163.5, 164.8 and 171.5 ppm.

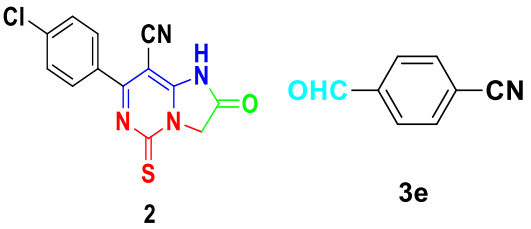
The existence of O-H, N-H, C≡N, C=O, and C=S functions in the IR data of **4f** validates its structure at 3353, 3185, 2190, 1697, and 1317 cm^{-1}, respectively. The imidazopyrimidine **4f** ^{1}H -NMR spectrum revealed four singlets at δ_H 3.94, 6.31, 12.60 and 12.99 for methoxy group, benzylidene (=CH), OH and N-H protons, respectively. Furthermore, at δ_H 7.13, 7.23-7.33 and 7.38 ppm, the two aryl rings divide into two doublets and one multiplet. The **4f** ^{13}C-NMR spectra accounted for 19 signals at 52.07, 57.01, 118.9, 119.7, 121.9, 122.2, 123.5, 124.4, 125.6, 129.1, 129.5, 129.7, 130.0, 131.5, 146.4, 151.3, 162.6, 166.4 and 173.0 ppm for sp^3, sp^2 and sp carbons.

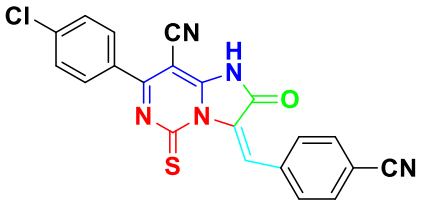


Scheme 2: Formation of chalcone linker via condensation reaction between imidazo[1,2-*c*]pyrimidine and aldehydes.

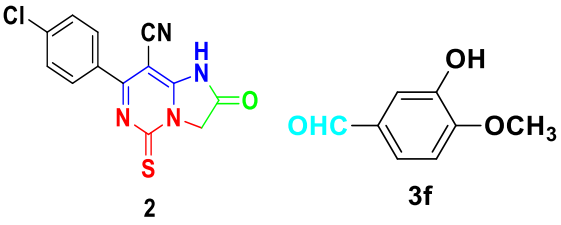
Table 1: Chemical structure of imidazo[1,2-*c*]pyrimidine and aldehydes fragments and the hybrid products.

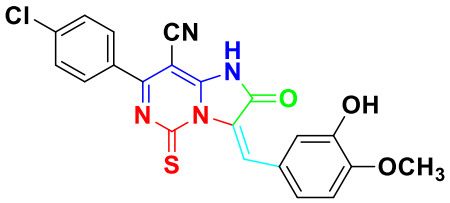
Entry	imidazopyrimidine	Aldehydes	Hybrid products (yield %)
1	 2	 3a	 **4a** (98%)
2	 2	 3b	 **4b** (87%)
3	 2	 3c	 **4c** (92%)
4	 2	 3d	 **4d** (85%)





4e (96%)





4f (97%)

Assessment antimicrobial activity:

The antimicrobial activity of the synthesized compounds **4a-f** was tested against two gram-positive bacteria (*Staphylococcus aureus, Bacillus subtilis*), two gram-negative bacteria (*Escherichia coli, Pseudomonas aeuroginosa*), and two fungi (*Candida albicans, Aspergillus flavus*) obtained from the Faculty of Pharmacy, Mansoura University, Egypt. The disc diffusion technique, as reported in the literature **[26]**, was employed to assess the antimicrobial activity of synthesized compounds. In this study, the results were compared to the activity of commercially available conventional antibiotics (Ampicillin and Colitrimazole). The results are shown in (Table 2).

Table (2): Antimicrobial Activities of compounds (4a-f).

Compound	*E. coli*		*P.aeuroginosa*		*S. aureus*		*B. subtilis*		*C. Albicans*		*A. flavus*	
	Diameter of inhibition zone (mm)	% Activity index	Diameter of inhibition zone (mm)	% Activity index	Diameter of inhibition zone (mm)	% Activity index	Diameter of inhibition zone (mm)	% Activity index	Diameter of inhibition zone (mm)	% Activity index	Diameter of inhibition zone (mm)	% Activity index
4a	9	36	12	52.17	13	54.16	11	47.82	12	44.44	8	32
4b	12	48	15	65.22	17	70.83	16	69.57	19	70.37	13	52
4c	8	32	13	56.52	15	62.5	15	65.22	16	59.26	10	40
4d	6	24	4	17.39	NA	----	5	21.74	10	37.04	7	28
4e	NA	----	6	26.09	3	12.5	4	17.39	5	18.52	NA	----
4f	16	64	18	78.26	21	87.5	19	82.61	17	62.96	12	48
Ampicillin	25	100	23	100	24	100	23	100	NA	----	NA	----
Colitrimaz-ole	NA	----	NA	----	NA	----	NA	----	27	100	25	100

- NA → No Activity.

According to the results were recorded in **Table (2)**, the synthesized compounds showed antibacterial activity against *P. aeruginosa and B. subtilis*, while only compounds (**4a-d** and **4f**) displayed activity against *E. coli*. Furthermore, only compounds (**4a-c, 4e** and **4f**) reduced the development of *S. aureus*. With regards to *E. coli*, **4f** displayed the highest antibacterial activity (16 mm), followed by **4b** (12 mm), **4a** (9 mm), **4c** (8 mm) and **4d** (6 mm). Also, **4f** revealed significant antibacterial activity against *P. aeruginosa* (18 mm) compared to **4b** (15 mm), **4c** (13 mm), **4a** (12 mm), **4e** (6 mm) and **4d** (4 mm). Only compounds (**4f**, **4b**, **4c**, **4a** and **4e**) displayed activity against *S. aureus* (21, 17, 15, 13 and 3 mm), respectively. On the other hand, the compounds (**4f**, **4b**, **4c**, **4a**, **4d** and **4e**) exhibited antibacterial activity against *B. subtilis* (19, 16, 15, 11, 5 and 4 mm), respectively.

Furthermore, the compounds (**4b**, **4f**, **4c, 4a**, **4d and 4e**) had antifungal activity against *C. Albicans* (19, 17, 16, 12, 11, 10 and 5 mm), respectively. Also, compounds (**4b**, **4f**, **4c**, **4a and 4d**) displayed activity against A. *flavus* (13, 12, 10, 8 and 7 mm), respectively.

Moreover, **4b** had strong antibacterial activity against *P. aeruginosa* (65.22%), *S.aureus* (70.83%) and *B. subtilis* (69.57 %), and moderate against *E.coli* (48%),while **4c** showed strong antimicrobial activity against *S.aureus* (62.5%) and *B. subtilis* (65.22%) and moderate against *E.coli* (32%), *P. aeruginosa* (56.52%). Furthermore, **4a** showed moderate antibacterial activity against *E.coli* (36%), *P. aeruginosa* (52.17%), *S.aureus* (54.16%) and *B. subtilis* (47.82%). Also, **4d** showed weak antibacterial activity against *E.coli* (24%), *P. aeruginosa* (17.39%) and *B. subtilis* (21.74%). With regards to **4e** showed weak antimicrobial activity against *P. aeruginosa* (26.09 %), *S.aureus* (12.5 %) and *B. subtilis* (17.39%). In addition, **4f** had strong antibacterial activity against *E.coli* (64%), *P. aeruginosa* (78.26%), *S.aureus* (87.5%) and *B. subtilis* (82.61 %) when compared to Ampicillin.

With regards to *C. Albicans*, the compounds (**4b**, **4c and 4f**) showed strong antifungal activity (70.37 %, 59.26 % and 62.96%), respectively, while the compounds (**4a**, **4d and 4e**) showed weak antifungal activity (44.44 %, 37.04% and 18.52%), respectively. Also, the compounds (**4b and 4f**) showed moderate antifungal activity against *A. flavus* (52 % and 48%), respectively, while the compounds (**4c, 4a and 4d**) showed weak antifungal activity (40%, 32 % and 28%), respectively, when compared to Colitrima-zole.

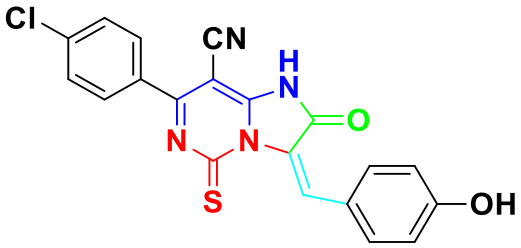
III. Experimental

Melting points were determined using an Electro-thermal IA 9100 equipment. On a Nexus 670 FTIR Nicolet, Fourier transform infrared spectrometer, IR spectra (KBr) were obtained. The ^{1}H and ^{13}C NMR spectra were measured in DMSO-d_6 using a JEOL-JNM-LA 400 MHz spectrometer for ^{1}H NMR and a JEOL-JNM-LA 100 MHz spectrometer for ^{13}C NMR. TMS is the industry standard for expressing chemical changes on the (ppm) scale. TLC was detected using UV light on Merck Silica Gel 60F254. At Cairo University's Microanalysis Centre, element analysis was done using a PerkinElmer 240 (microanalysis). The chemicals and solvents used in the synthesis of imidazo[1,2-*c*] pyrimidine derivatives were given by Merck and Aldrich. Compounds **2** and **3** are synthesized and analyzed in the same manner as stated before **[24, 25].**

General method for synthesis of target imidazo[1,2-*c*]pyrimidines 4a-f

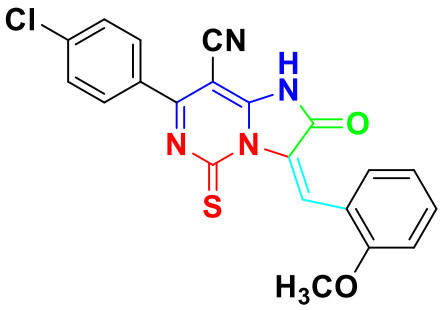
A solution of imidazole **2** (0.01 mol) and aromatic aldehyde **3** namely, 4-hydroxybenzaldehyde, 2-methoxybenzaldehyde, 2-tolualdehyde, 3-nitrobenzaldehyde, 4-cyanobenzaldehyde and 3-hydroxy-4-methoxybenzaldehyde (0.01 mol) in absolute ethanol was stirred at room temperature for 30-90 minutes (TLC indicator) in the presence of K_2CO_3-NPs (0.01 mol). After the reaction was completed, the mixture was cooled and diluted with cold H_2O, and the resulting product was filtered, dried, and recrystallized from ethanol.

7-(4-Chlorophenyl)-3-(4-hydroxybenzylidene)-2-oxo-5-thioxo-1,2,3,5-tetrahydroimidazo[1,2-*c*]pyrimidine-8-carbonitrile (4a)



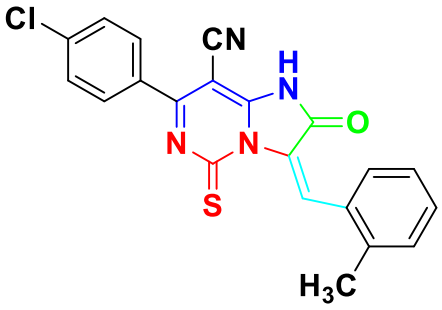
Yellow powder, mp 308-310 ^{o}C; yield: 98 %. IR (νmax, cm-1): 3450 (O-H), 3245 (N-H), 2193 (C≡N), 1676 (C=O), 1298 (C=S). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 6.79 (s, 1H, =CH), 7.22 (d, 2H, ^{3}J = 8.40 Hz, H_{aryl}), 7.44 (d, 2H, ^{3}J = 8.80 Hz, H_{aryl}), 7.63 (d, 2H, ^{3}J = 8.80 Hz, H_{aryl}), 7.71 (d, 2H, ^{3}J = 7.20 Hz, H_{aryl}), 10.49 (s, 1H, OH, exchange with D_2O), 11.51 (s, 1H, NH, exchange with D_2O). ^{13}C NMR, δ = 52.45, 113.9, 114.9, 118.3, 118.5, 126.0, 126.8, 127.3, 134.3, 135.8, 142.8, 152.4, 158.2, 163.5, 164.8 and 171.5. Anal. Calcd for $C_{20}H_{11}ClN_4O_2S$ (406.84): C, 59.04; H, 2.73; N, 13.77 %. Found: C, 58.95; H, 2.75; N, 13.82

7-(4-Chlorophenyl)-3-(2-methoxybenzylidene)-2-oxo-5-thioxo-1,2,3,5-tetrahydroimidazo[1,2-*c*]pyrimidine-8-carbonitrile (4b)



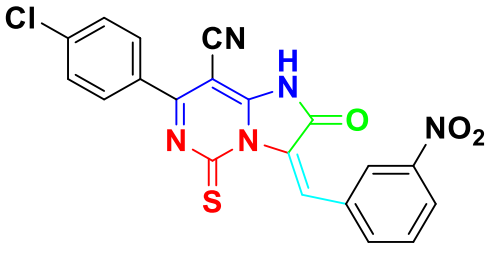
Yellow powder, mp 305-307 °C; yield: 87 %. IR (ν_{max}, cm^{-1}): 3320 (N-H), 2191 (C≡N), 1656 (C=O), 1301 (C=S). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 3.92 (s, 3H, OCH_3), 6.58 (s, 1H, =CH), 7.38 (t, 2H, ^3J = 7.20 Hz, H_{aryl}), 7.42 (d, 2H, ^3J = 7.60 H_Z, H_{aryl}), 7.51 (d, 2H, ^3J = 6.80 H_Z, H_{aryl}), 7.60 (d, 2H, ^3J = 9.60 H_Z, H_{aryl}), 10.99 (s, 1H, NH, exchange with D_2O). ^{13}C NMR, δ = 52.62, 54.82, 114.7, 115.8, 120.0, 126.6, 128.9, 130.2, 130.8, 131.8, 141.7, 148.2, 154.2, 159.8, 164.3 and 171.7. Anal. Calcd for $C_{21}H_{13}ClN_4O_2S$ (420.87): C, 59.93; H, 3.11; N, 13.31 %. Found: C, 59.82; H, 3.09; N, 13.37.

7-(4-Chlorophenyl)-3-(2-methylbenzylidene)-2-oxo-5-thioxo-1,2,3,5-tetrahydroimidazo[1,2-*c*]pyrimidine-8-carbonitrile (4c)



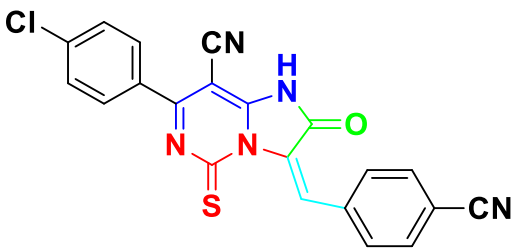
Pale yellow powder, mp 302-304 °C; yield: 92 %. IR (ν_{max}, cm^{-1}): 3185 (N-H), 2191 (C≡N), 1658 (C=O), 1211 (C=S). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 2.69 (s, 3H, CH_3), 4.61 (s, 1H, =CH), 7.17 (t, 1H, ^3J = 8.40 Hz, H_{aryl}), 7.29 (t, 1H, ^3J = 8.00 H_Z, H_{aryl}), 7.44 (d, 2H, ^3J = 8.00 H_Z, H_{aryl}), 7.64 (d, 2H, ^3J = 8.40 H_Z, H_{aryl}), 7.76 (d, 2H, ^3J = 8.00 H_Z, H_{aryl}), 10.97 (s, 1H, NH, exchange with D_2O). ^{13}C NMR, δ = 25.12, 50.92, 115.5, 120.4, 128.9, 129.1, 130.1, 130.5, 131.6, 135.1, 140.0, 144.3, 151.1, 160.0, 163.1 and 171.1. Anal. Calcd for $C_{21}H_{13}ClN_4OS$ (404.87): C, 62.30; H, 3.24; N, 13.84 %. Found: C, 62.21; H, 3.27; N, 13.89.

7-(4-Chlorophenyl)-3-(3-nitrobenzylidene)-2-oxo-5-thioxo-1,2,3,5-tetrahydroimidazo[1,2-*c*]pyrimidine-8-carbonitrile (4d)



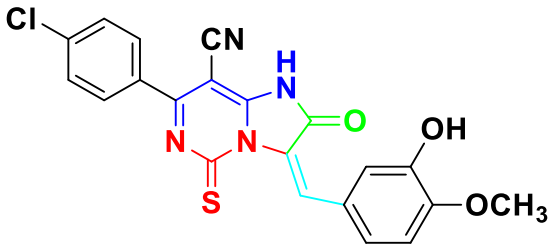
Pale brown powder, mp 311-313 °C; yield: 85 %. IR (ν_{max}, cm^{-1}): 3236 (N-H), 2192 (C≡N), 1692 (C=O), 1292 (C=S). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 5.17 (s, 1H, =CH), 7.03 (s, 1H, H_{aryl}), 7.11 (t, 1H, ^3J = 8.40 H_Z, H_{aryl}), 7.21 (d, 2H, ^3J = 8.80 H_Z, H_{aryl}), 7.43 (d, 2H, ^3J = 9.60 H_Z, H_{aryl}), 7.62 (d, 2H, ^3J = 7.60 H_Z, H_{aryl}), 9.57 (s, 1H, NH, exchange with D_2O). ^{13}C NMR, δ = 52.42, 115.4, 120.4, 123.3, 131.3, 131.4, 132.5, 132.8, 133.9, 135.0, 144.4, 148.4, 149.9, 150.3, 160.8, 163.3 and 175.5. Anal. Calcd for $C_{20}H_{10}ClN_5O_3S$ (435.84): C, 55.12; H, 2.31; N, 16.07 %. Found: C, 55.21; H, 2.28; N, 16.14.

7-(4-Chlorophenyl)-3-(4-cyanobenzylidene)-2-oxo-5-thioxo-1,2,3,5-tetrahydroimidazo[1,2-*c*]pyrimidine-8-carbonitrile (4e)



Yellow powder, mp 314-316 ^{o}C; yield: 96 %. IR (ν_{max}, cm^{-1}): 3371 (N-H), 2194 (C≡N), 1666 (C=O), 1296 (C=S). ^{1}H NMR (400 MHz, DMSO-d$_6$): δ_H = 5.09 (s, 1H, =CH), 7.38 (d, 2H, ^{3}J = 7.20 Hz, H$_{aryl}$), 7.42 (d, 2H, ^{3}J = 7.60 H$_Z$, H$_{aryl}$), 7.44 (d, 1H, ^{3}J = 7.60 H$_Z$, H$_{aryl}$), 7.46 (d, 1H, ^{3}J = 7.20 H$_Z$, H$_{aryl}$), 7.51 (d, 1H, ^{3}J = 7.20 H$_Z$, H$_{aryl}$), 7.61 (d, 1H, ^{3}J = 8.40 H$_Z$, H$_{aryl}$), 11.41 (s, 1H, NH, exchange with D$_2$O). ^{13}C NMR, δ = 55.95, 114.8, 117.1, 128.3, 129.4, 130.4, 130.6, 131.8, 142.0, 142.1, 142.2, 151.4, 157.3, 161.4, 168.6 and 171.6. Anal. Calcd for $C_{21}H_{10}ClN_5OS$ (415.86): C, 60.65; H, 2.42; N, 16.84 %. Found: C, 60.72; H, 2.45; N, 16.91.

7-(4-Chlorophenyl)-3-(3-hydroxy-4-methoxybenzylidene)-2-oxo-5-thioxo-1,2,3,5-tetrahydroimidazo[1,2-*c*]pyrimidine-8-carbonitrile (4f)



Yellow powder, mp 318-320 ^{o}C; yield: 97 %. IR (ν_{max}, cm^{-1}): 3353 (O-H), 3185 (N-H), 2190 (C≡N), 1697 (C=O), 1317 (C=S). ^{1}H NMR (400 MHz, DMSO-d$_6$): δ_H = 3.94 (s, 3H, OCH$_3$), 6.31 (s, 1H, =CH), 7.13 (d, 2H, ^{3}J = 7.60 Hz, H$_{aryl}$), 7.23-7.33 (m, 3H, H$_{aryl}$), 7.38 (d, 2H, ^{3}J = 8.40 H$_Z$, H$_{aryl}$), 12.60 (s, 1H, OH, exchange with D$_2$O), 12.99 (s, 1H, NH, exchange with D$_2$O). ^{13}C NMR, δ = 52.07, 57.01, 118.9, 119.7, 121.9, 122.2, 123.5, 124.4, 125.6, 129.1, 129.5, 129.7, 130.0, 131.5, 146.4, 151.3, 162.6, 166.4 and 173.0. Anal. Calcd for $C_{21}H_{13}ClN_4O_3S$ (436.87): C, 57.74; H, 3.00; N, 12.82 %. Found: C, 57.82; H, 3.10; N, 12.80.

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