A CONVENIENT SYNTHESIS OF [1,2,4]TRIAZOLO[1,5-A]PYRIDINES AND 1,8-NAPHTHYRIDINE OF ANALGESIC AND ANTI-INFLAMMATORY PROFILES

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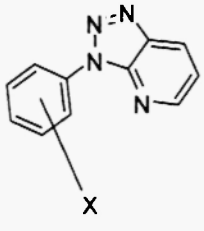
Abstract: Starting from 1,6-diamino-3,5-dicyano-4-aryl-2-pyridones, substituted triazolo[1,5-a]pyridines and 1,8-naphthyridine derivatives have been synthesized. All the synthesized compounds were fully characterized by spectroscopic, physical data, and elemental analyses. Some of triazolo[1,5-a]pyridines were tested with respect to their analgesic and anti-inflammatory activities. All tested compounds exhibited analgesic activities comparable or superior to Valdecoxib. The anti-inflammatory activity was present in all the tested compounds as well and exceeded that of Hydrocortisone.

Keywords: Triazolopyridines, Analgesic, Anti-inflammatory.

Introduction:

Pyridines have been reported as biologically interesting molecules [1-4] and precursors for the synthesis of triazolo[1,5-a]pyridines. Several methods have previously described the synthesis of triazolo[1,5-a]pyridines from 1,6-damino pyridines [5-9]. Moreover, triazolo[1,5-a]pyridines are reported to be useful compounds as pharmaceuticals [10], fluorescent brighteners [11] and complexing agents [12]. Their synthesis usually involves several steps, and either the pyridine ring [6,7,13,14] or the triazole [15] ring can be constructed first. Triazolo[1,5-a]pyridines have also been prepared by ring transformation of triazolo[4,3-a]pyridines [16] and from 2-thioxopyrones [17].

The analgesic activity of many 3-(substituted phenyl)triazolo[4,5-b]pyridines (I) was reported by researchers in *Merck Sharp & Dohme Laboratories*[18].

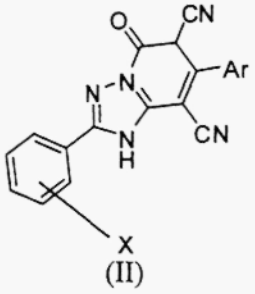


I

Some of the prepared compounds were reported to be superior in analgesic activity to codeine and d-propoxyphene without showing any narcotic characteristics. Some of the compounds also possessed activity against Carrageenan-induced foot edema in the rat.

In the present investigation, the synthesis of some triazolo[1,5-a]pyridines and their related derivatives was attempted. Some of the prepared compounds, which have

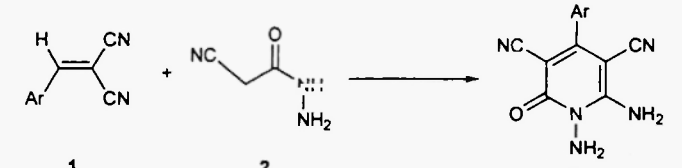
some structural similarity to the above mentioned triazolopyridines (I), were investigated with respect to their analgesic and anti-inflammatory activity. The tested compounds have the following general structure (II):



(II)

Results and Discussion:

1,6-diamino-3,5-dicyano-4-aryl-2-pyridones **3a-e**, the precursor [19] of the present investigation, was prepared in a good yield by reacting the appropriate arylidenemalononitrile **2** with cyanoaceto hydrazide **1**. The reaction is easily performed in ethanol at room temperature by stirring a mixture of **1** and **2** for 5 hours in the presence of a catalytic amount of piperidine (Scheme 1).



1
a, Ar= 3-OCH3-Ph
b, Ar= 2-Br-Ph
c, Ar= 3,4-di-Cl-Ph
d, Ar= 3,4-di-OCH3 Ph
e, Ar= 2,5-di-OCH3-Ph

2

3
a, Ar= 3-OCH3-Ph
b, Ar= 2-Br-Ph
c, Ar= 3,4-di-Cl-Ph
d, Ar= 3,4-di-OCH3 Ph
e, Ar= 2,5-di-OCH3-Ph

Scheme (1)

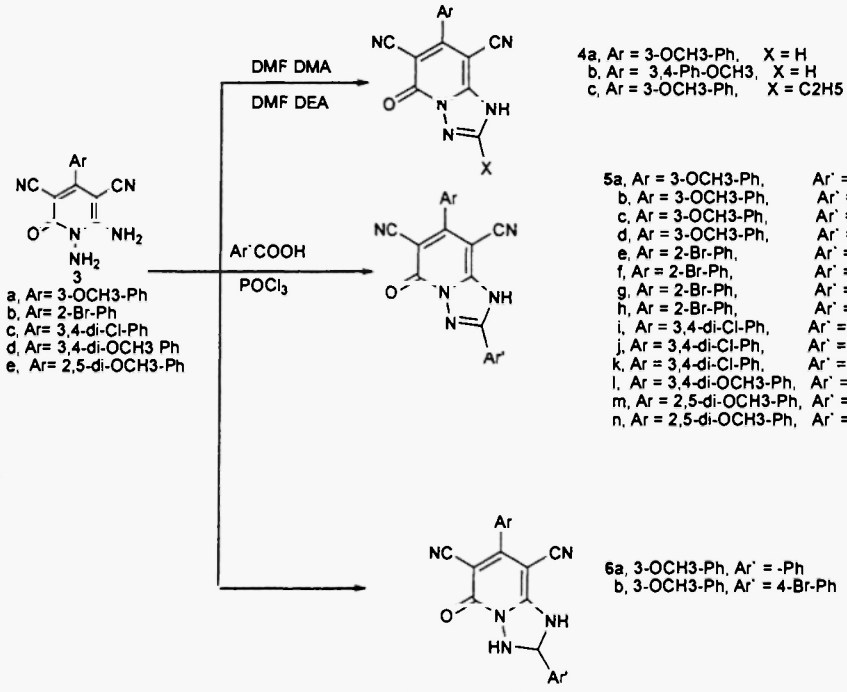
A series of 1,6-diamino-3,5-dicyano-4-aryl-2-pyridones **3a-e** is thus obtained in good yields. The nature of the substituent present on the benzene ring of the benzylidene malononitrile has little effect on the time of reaction.

Cyclization of **3** with dimethyl formamide dialkyl acetal (DMF DMA, DMF DEA) at room temperature afforded 7-(aryl)-5-oxo-1,5-dihydro[1,2,4]triazolo[1,5-*a*]pyridine-6,8-dicarbonitriles **4a-c** in good yields. The ^{1}H-NMR of **4a** as an example showed broad signal at 11.3 ppm corresponding to NH, and other signals at 3.85(s,3H), 7.3(d,1H), 7.45(dd, 2H) and 7.65(t,1H), the IR spectrum of **4a** also revealed the presence of cyano group at 2210, 1655 (C=O), 3127(NH).

We reported in this paper a new and simple route to the formation of triazolo[1,5-a]pyridines **5a-n** by the reaction of appropriate carboxylic acids with **3**. The reaction is easily performed in phosphorus oxychloride as medium under reflux for 5 hours. ^{1}H-NMR data of the resulting triazolo[1,5-a]pyridines **5a-n** revealed the disappearance of NH_2 protons signals and appearance of NH proton signal at 11.1-11.7. On the other hand, the IR spectrum of **5k** as an example revealed the presence of two signals at 1350 and 1550 corresponding to NO_2 group symmetric and asymmetric vibrations.

To the best of our knowledge, there is only one precedent in the literature[8] in which a condensation of N-aminopyridone with aromatic aldehyde in dioxane containing piperidine as a catalyst formed piperidinium salt of the corresponding triazolopyridine[8,20].

Unexpectedly, upon reacting the pyridine derivative **3a** with aromatic aldehydes in absence of piperidine under reflux, the dihydrotriazolopyridine derivatives **6a,b** were smoothly isolated, rather than the expected products (piperidinium salts). ^{1}H-NMR spectrum of **6a** revealed the coupling of triazole protons.



Scheme (2)

These results were extended to study the reactivity of aldohexose as D-xylose with **3a** affording **7** (scheme 3) which showed NH protons of the triazole ring at 8.4 and 11.9 and the CH proton of the triazole ring at 4.9 while the protons of the sugar moiety appeared in the range of 3-5 ppm.

As a continuation for our approach to synthesize new derivatives of triazolopyridines using variety of reagents, the reaction of **3a** with ethyl cyanoacetate took place affording unexpected product. The ^{1}H-NMR spectrum showed two amino groups in 5-6 region and 8.4 region respectively.

These results didn't coincide with the proposed structure **8** and at the same time, it cannot fit with the formation of a diazepine ring **9** which is more unlikely. However, this result agrees with the structure **10** as a result of 1,2 shift.

On the other hand, formation of structure **8** occurred as a result of the reaction of cyanoacetic acid and **3a** in $POCl_3$ under reflux.

Reaction of key precursor **3a** with bis(methylthio)cyanamide by refluxing in ethanol afforded [6,8-dicyano-7-(3-methoxyphenyl)-5-oxo-1,5-dihydro[1,2,4]triazolo[1,5-*a*]pyridin-2-yl]cyanamide **11**.

The results prompted us to react **3** with [bis(methylthio)methylene]malononitrile and methyl-2-cyano-3,3-bis(methylthio)acrylate by refluxing in ethanol to afford 2-(dicyanomethylene)-7-(3-methoxyphenyl)-5-oxo-,2,3,5-tetrahydro[1,2,4]triazolo[1,5-*a*]pyridine-6,8-dicarbonitrile **12a** and methyl (2)-cyano[6,8-dicyano-7-(3-methoxyphenyl)-5-oxo-1,5-dihydro[1,2,4]triazolo[1,5-*a*]pyridin-2(3*H*)-ylidene]acetate **12b** respectively.

The aforementioned results encouraged us to study the reactivity of benzoyl acetonitrile to synthesize the title compound pyridopyridine **13**. These results support that NH_2 is more basic than N-NH_2.

Experimental:

Melting points are uncorrected and were taken on a Boetius melting point microscope. Microanalyses were performed by the micro analytical unit at Cairo University. IR spectra were recorded on a Mattson 5000 FIR spectrometer. ^{1}HNMR spectra were determined on a Varian EMNMR spectrometer using tetramethylsilane as an internal standard. Mass spectra (MS) were recorded on a Finigan SSQ 7000 Mass spectrometer.

1,6-diamino-2-oxo-4-aryl-1,2-dihydropyridine-3,5-dicarbonitrile (3a-e): A mixture of **1** (0.02 mole) and **2** (0.01 mole) in absolute ethanol (25 ml) containing catalytic amount of piperidine was allowed to stir for 5 hours at room temperature. The resulting precipitate was filtered off, washed several times with ethanol and crystallized to afford compounds **3a-e**.

7-(Aryl)-5-oxo-1,5-dihydro[1,2,4]triazolo[1,5-*a*]pyridine-6,8-dicarbonitrile (4a-c): A mixture of equimolar amounts of **3a,b** and DMF was refluxed for 3 hours in ethanol (25 ml). The precipitate formed was filtered off, washed several times with ethanol and crystallized from aqueous DMF to afford **4a-c**.

7,2-Diaryl-5-oxo-1,5-dihydro[1,2,4]triazolo[1,5-a]pyridine-6,8-dicarbonitriles (5a-n): A mixture of equimolar amounts of **3a-e** and the corresponding aromatic acids in freshly distilled $POCl_3$ was refluxed for 3 hours. The resulting dark brown syrupy liquid was poured onto a beaker filled with crushed ice. The resulting solid was filtered off and crystallized from proper solvent to afford **5a-n**.

2-Aryl-5-oxo-7-(3-methoxyphenyl -1,2,3,5- tetrahydro[1,2,4]triazolo[1,5-a]pyridine-6,8-dicarbonitriles (6a,b): A mixture of equimolar amounts of **3a** and the corresponding aldehyde in ethanol was allowed to reflux for eleven hours. The resulting precipitate was filtered off, washed several times with ethanol and crystallized from glacial acetic acid to afford **6a,b**.

7-(3-Methoxyphenyl)-5-oxo-2-((1S,2R,3R)-1,2,3,4-tetrahydroxybutyl)-1,2,3,5-tetrahydro-[1,2,4]triazolo[1,5-a]pyridine-6,8-dicarbonitrile (7) A mixture of equimolar amounts of **3a** and D-Xylose was allowed to stir in ethanol (20 ml) for 12 hours at 60°C. The resulting precipitate was filtered off and crystallized from dioxane to afford 60% of **7.**

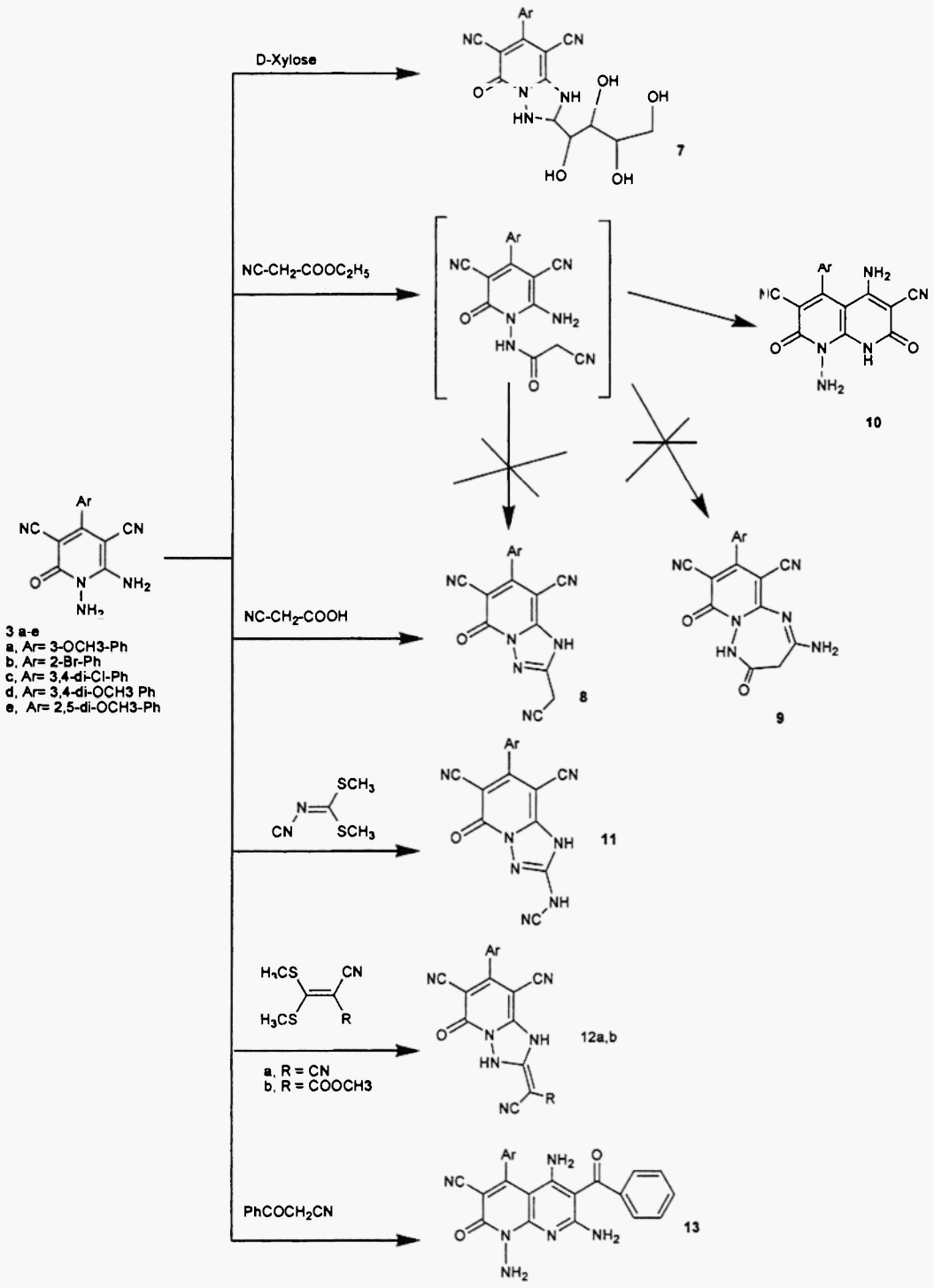
2-Cyanomethyl-7-(3-methoxyphenyl)-5-oxo-1,5-dihydro[1,2,4]triazolo[1,5-a]pyridine-6,8-dicarbonitrile (8) Equimolar amounts of **3a** and cyanoacetic acid were allowed to reflux in $POCl_3$ for 3 hours. The reaction mixture was then crystallized from glacial acetic acid to afford 60% of **8.**

1,5-Diamino-4-(3-methoxyphenyl)-2,7-dioxo-1,2,7,8-tetrahydro-1,8-naphthyridine-3,6-dicarbonitrile (10) Compound **3a** (0.01 mole) was allowed to reflux in the presence of ethyl cyanoacetate (20 ml) for 6 hours. The resulting precipitate was filtered off and crystallized from glacial acetic acid to afford 80% of **10**.

[6,8-dicyano-7-(3-methoxyphenyl)-5-oxo-1,5-dihydro[1,2,4]triazolo[1,5-*a*]pyridin-2-yl]cyanamide (11)

A mixture of equimolar amounts of **3a** and dimethyl cyanodithioimidocarbonate was allowed to reflux for 5 hours in ethanol (20 ml). The resulting precipitate was filtered off, washed several times with ethanol and crystallized from DMF to afford 81% of **11.**

2-(dicyanomethylene)-7-(3-methoxyphenyl)-5-oxo-1,2,3,5-tetrahydro[1,2,4] triazolo-[1,5-*a*]pyridine-6,8-dicarbonitrile (12a) and **Methyl(2*E*)-cyano[6,8-dicyano-7-(3-methoxyphenyl)-5-oxo-1,5-dihydro[1,2,4]triazolo[1,5-*a*]pyridin-2(3*H*)-ylidene]acetate (12b)** A mixture of equimolar amounts of **3a** and bis(methylthio)methylene]malononitrile or methyl-2-cyano-3,3-bis(methylthio)acrylate was allowed to reflux in ethanol for 10 hours. The resulting precipitate was filtered off, washed several times with ethanol and crystallized from DMF to afford 77% of **12a** and 72% of **12b** respectively.



(Scheme 3)

1,5,7-triamino-6-benzoyl-4-(3-methoxyphenyl)-2-oxo-1,2-dihydro-1,8 naphthyridine-3-carbonitrile (13) A mixture of equimolar amounts of **3a** and benzoyl acetonitrile was dissolved in 20 ml ethanol/DMF mixture (1:1 ratio). A few drops of piperidine were added and the reaction mixture was allowed to reflux for 10

hours and then evaporated under vacuum affording gummy material which upon washing several times with ethanol afforded 67% of **13.**

Table 1. Physical and analytical data of newly prepared compounds:

Comp. No.	*Yield %*	*m.p. °C (solvent)*	*Mol. formula (M.wt.)*	*Analysis Calculated/Found* C%	H%	N%
3a	95	267-9 (Methanol)	$C_{14}H_{11}N_5O_2$ (281.27)	59.78 59.81	3.94 3.98	24.90 24.88
3b	90	288-9 (Methanol)	$C_{13}H_8BrN_5O$ (330.14)	47.29 47.33	2.44 2.47	21.21 21.19
3c	88	311-2 (Methanol)	$C_{13}H_7Cl_2N_5O$ (320.13)	48.77 48.74	2.20 2.17	21.88 21.85
3d	86	260-1 (Methanol)	$C_{15}H_{13}N_5O_3$ (311.30)	57.87 57.89	4.21 4.24	22.50 22.54
3e	80	266-2 (Methanol)	$C_{15}H_{13}N_5O_3$ (311.30)	57.87 57.90	4.21 4.19	22.50 22.46
4a	81	288-2 (aqueous DMF)	$C_{19}H_9N_5O_2$ (291.26)	61.85 61.81	3.11 3.21	24.04 24.01
4b	85	292-3 (aqueous DMF)	$C_{16}H_{11}N_5O_3$ (321.29)	59.81 59.84	3.45 3.43	21.80 21.84
4c	79	287-8 (aqueous DMF)	$C_{17}H_{13}N_5O_2$ (319.32)	63.94 63.96	4.10 4.13	21.93 21.97
5a	70	286-8 (Ethanol)	$C_{21}H_{12}BrN_5O_2$ (446.26)	56.52 56.55	2.71 2.74	15.69 15.71
5b	72	260-1 (Ethanol)	$C_{21}H_{13}N_5O_2$ (367.36)	68.66 68.63	3.57 3.60	19.06 19.03
5c	71	223-5 (Ethanol)	$C_{21}H_{12}ClN_5O_2$ (401.81)	62.77 62.74	3.01 2.99	17.43 17.39
5d	69	201-2 (Ethanol)	$C_{22}H_{15}N_5O_2$ (381.39)	69.28 69.30	3.96 4.00	18.36 18.39
5e	69	195-7 (Ethanol)	$C_{20}H_9Br_2N_5O$ (495.13)	48.52 48.55	1.83 1.86	14.14 14.10
5f	68	205-7 (Aqueous Ethanol)	$C_{20}H_{10}BrN_5O$ (416.23)	57.71 57.74	2.42 2.39	16.83 16.80
5g	66	178-9 (Ethanol)	$C_{20}H_9BrClN_5O$ (450.68)	53.30 53.34	2.01 1.99	15.54 15.51
5h	64	140-1 (Ethanol)	$C_{21}H_{12}BrN_5O$ (430.26)	58.62 58.61	2.81 2.84	16.28 16.31
5i	67	>300 (Ethanol)	$C_{20}H_8Cl_3N_5O$ (440.67)	54.51 54.54	1.83 1.85	15.89 15.91
5j	63	266-8 (Ethanol)	$C_{21}H_{11}Cl_2N_5O$ (420.25)	60.02 60.06	2.64 2.66	16.66 16.69
5k	64	263-5 (Ethanol)	$C_{20}H_8Cl_2N_6O_3$ (451.22)	53.24 53.28	1.79 1.82	18.62 18.66
5l	61	208-9 (Ethanol)	$C_{22}H_{15}N_5O_3$ (397.39)	66.49 66.53	3.80 3.84	17.62 17.59
5m	58	190-2 (Ethanol)	$C_{22}H_{11}BrN_5O_3$ (476.28)	55.48 55.50	2.96 2.95	14.70 14.67
5n	56	220-1 (Ethanol)	$C_{22}H_{14}ClN_5O_3$ (431.83)	61.19 61.22	3.27 3.30	16.22 16.18
6a	80	280-2 (Glacial acetic acid)	$C_{21}H_{15}N_5O_2$ (369.38)	68.28 68.31	4.09 4.11	18.96 19.00
6b	78	>300 (Glacial	$C_{21}H_{14}BrN_5O_2$ (448.27)	56.27 56.25	3.15 3.14	15.62 15.59

		acetic acid)				
7	60	142-4 (Dioxane)	$C_{19}H_{19}N_5O_6$ (413.38)	55.20 55.35	4.63 4.66	16.94 16.97
8	60	295-7 (Glacial acetic acid)	$C_{17}H_{10}N_6O_2$ (330.30)	61.82 61.85	3.05 3.00	25.44 25.48
10	80	240-1 (Glacial acetic acid)	$C_{17}H_{12}N_6O_3$ (348.32)	58.62 58.66	3.47 3.50	24.13 24.10
11	81	>300 (DMF)	$C_{16}H_9N_7O_2$ (331.29)	58.01 58.22	2.74 2.76	29.60 29.64
12a	77	>300 (DMF)	$C_{18}H_9N_7O_2$ (355.31)	60.85 60.83	2.55 2.52	27.59 27.63
12b	72	>300 (DMF)	$C_{19}H_{12}N_6O_4$ (388.34)	58.76 58.80	3.11 3.13	21.64 21.68
13	67	>300 (DMF)	$C_{23}H_{18}N_6O_3$ (426.43)	64.78 64.73	4.25 4.29	19.71 19.74

Table 2. Spectral data (IR, M.S, and ^{1}HNMR) for the newly prepared compounds:

Comp. No.	IR (KBr) ν (cm^{-1})	M.S, EI m/z	^{1}HNMR (DMSO-d_6) δ (ppm)
3a	3200 (NH_2), 3250 (NH_2), 2215 (CN), 1680 (C=O), 1660 (C=C)	281 (M+, 100%)	3.1 (2H, s, N-NH_2), 3.84 (3H, s, OCH_3) (7.2-7.7) (4H, m, Ar-H), 8.4 (2H, s, NH_2).
3b	3200 (NH_2), 3260 (NH_2), 2210 (CN), 1680 (C=O), 1670 (C=C)		2.9 (2H, s, N-NH_2), (7.3-7.7) (4H, m, Ar-H), 8.9 (2H,s, NH_2).
3c	3220 (NH_2), 3270 (NH_2), 2200 (CN), 1675 (C=O), 1660 (C=C)		3.9 (2H, s, N-NH_2), (7.4-7.8) (3H, m, Ar-H), 8.7 (2H, s, NH_2).
3d	3245 (NH_2), 3320 (NH_2), 2212 (CN), 1665 (C=O), 1651(C=C)	311 (M+ 27.33%)	3.85 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 4.6 (2H, S, N-NH_2), (7.2-7.5) (3H, m, Ar-H), 8.8 (2H,s, NH_2).
3e	3230 (NH_2), 3277 (NH_2), 2210 (CN), 1677 (C=O), 1660 (C=C)		3.83 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 4.3 (2H, s, N-NH_2). (7.1-7.5) (3H, m, Ar-H), 8.6 (2H, s, NH_2).
4a	2210 (CN), 1655 (C=O), 3127(NH).		3.85 (3H, s, OCH_3), 7.3 (1H, d), 7.45 (2H, dd) and 7.65 (1H, t), 11.3 (1H, broad s, NH).
4b			3.9 (3H, s, OCH_3), 7.5-7.3(3H, m, Ar), 11.4(1H, broad s, NH).
4c	2200 (CN), 1675 (C=O), 3110(NH).		1.7 (3H, t, CH_3), 2.9 (2H, q, CH_2), 3.9 (3H, s, OCH_3), 7.39-7.61 (4H, m, Ar), 11.4 (1H, broad s, NH).
5a	3300(NH), 2218 (CN), 1710 (C=O), 1670 (C=C)	445 (M+, 17.01%), 447 (M+2, 15.07%)	3.8 (3H, s, OCH_3), 7.1-7.7 (4H, m, Ar-H), 7.2 (1H, d, Ar-H), 7.9 (1H, t, Ar-H), 8.2 (1H, d, Ar-H), 9 (1H, s, Ar-H) and 11.5 (1H, s, NH exchangeable with D_2O).
5b	3320(NH), 2203 (CN), 1713 (C=O), 1674 (C=C)	367.1 (M+, 15.68%)	3.8 (3H, s, OCH_3), 7.5-7.9 (6H, m, Ar-H) 7.2 (1H, d, Ar-H), 8.2 (1H, d, Ar-H), 9 (1H, s, Ar-H) ,and 11.7 (1H, s, NH exchangeable with D_2O).
5c	3320(NH), 2203 (CN), 1707 (C=O), 1664 (C=C)		3.8 (3H, s, OCH_3), 7.2-7.7 (8H, m, Ar-H), and 11.2 (1H, s, NH exchangeable with D_2O).
5d	3300(NH), 2215 (CN), 1716 (C=O), 1683(C=C)	381 (M+, 24.58%)	2.3 (3H, s, CH_3), 3.8 (3H, s, OCH_3), 7.3 (1H, d, Ar-H) 7.4-7.7 (4H, m, Ar-H), 8.1 (1H, d, Ar-H), 8.8 (1H, s, Ar-H) and 11.3 (1H, s, NH exchangeable with D_2O).

5e	3300(NH), 2203 (CN), 1710 (C=O), 1670 (C=C)		7.4-8 (8H, m, Ar-H), 11.2 (1H, s, NH exchangeable with D_2O).
5f	3320(NH), 2216(CN), 1713 (C=O), 1683(C=C)		7.3-8 (9H, m, Ar-H) and 11.3 (1H, s, NH exchangeable with D_2O).
5g	3300(NH), 2215 (CN), 1716 (C=O), 1690(C=C)		7.5-8 (7H, m, Ar-H), 9 (1H, d, Ar-H) and 11.3 (1H, s, NH exchangeable with D_2O).
5h	3300(NH), 2215 (CN), 1716 (C=O), 1683(C=C)		2.3 (3H, s, CH_3), 7.4-8 (8H, m, Ar-H) and 11.3 (1H, s, NH exchangeable with D_2O).
5i	3320(NH), 2216(CN), 1713 (C=O), 1683(C=C)		7.4-8. (6H, m, Ar-H) , 9 (1H, d, Ar-H), and 11.3 (1H, s, NH exchangeable with D_2O).
5j	3320(NH), 2216(CN), 1713 (C=O), 1683(C=C)		2.4 (3H, s, CH_3), 7.4-7.8 (7H, m, Ar-H) and 11.3 (1H, s, NH exchangeable with D_2O).
5k	3300(NH),2216(CN), 1710 (C=O), 1674 (C=C), 1350, 1550(NO2 symmetric, asymmetric)		7.5-7-9 (3 H, m, Ar-H), 8.2, 8.3 (2H, 2H; dd, J= 8Hz, p-disubstituted phenyl ring) and 11.7 (1H, s, NH exchangeable with D_2O).
5l	3320(NH), 2216(CN), 1713 (C=O), 1683(C=C)		3.7 (3H, s, OCH_3), 3.8 (3H, s, OCH_3), 7.3-8 (8H, m, Ar-H) 11.3 (1H, s, NH exchangeable with D_2O).
5m	3320(NH), 2216(CN), 1713 (C=O), 1683(C=C)		3.7 (3H, s, OCH_3), 3.8 (3H, s, OCH_3), 7.5-7.7 (7H, m, Ar-H) 11.3 (1H, s, NH exchangeable with D_2O).
5n	3320(NH), 2216(CN), 1713 (C=O), 1683(C=C)		3.7 (3H, s, OCH_3), 3.8 (3H, s, OCH_3), 7.5-7.8 (6H, m, Ar-H), 8.2 (1H, d, Ar-H) 11.3 (1H, s, NH exchangeable with D_2O).
6a	3300(NH), 3320(NH), 2216(CN), 1713 (C=O), 1683(C=C)	369 (M+, 24.67%)	3.8 (3H, s, OCH_3), 6.3 (1H, d, benzylic proton of the triazole ring) 7.3-8 (9H, m, Ar-H) 8.5 (1H, s, NH exchangeable with D_2O) and 10.9 (1H,s, NH exchangeable with D_2O).
6b	3300(NH), 3310(NH), 2210(CN), 1695 (C=O), 1680(C=C)		3.8 (3H, s, OCH_3), 6.3 (1H, d, benzylic proton of the triazole ring) 7.85, 8.1 (2H, 2H; dd, J= 7Hz, p-disubstituted phenyl ring), 7.2-7.7 (3H, m, Ar-H). 9 (1H, s, Ar-H) 10.9 (1H, s, NH exchangeable with D_2O) and 11 (1H, s, NH exchangeable with D_2O).
7	3400 (OH), 3300(NH), 3230(NH), 2200(CN), 1700 (C=O), 1685(C=C)		3.8 (3H, s, OCH_3) 4.9 (1H, d, J=13 CH proton of the triazole ring), 3-5 (protons of the sugar moiety), 7.3-7.8 (4H, m, Ar-H), 8.4 (1H, s, NH exchangeable with D_2O) and 11.8 (1H, s, NH exchangeable with D_2O)
8	3200(NH), 2210(CN), 2215 (CN), 1688 (C=O), 1660(C=C)		3.85 (3H, s, OCH_3), 4.2 (2H, s, CH_2), 7.2-7.6 (4H, m, Ar-H) and 11.1 (1H, s, NH)
10	3300(NH), 3250(NH_2), 3200(NH_2), 2210 (CN), 1670 (C=O), 1700 (C=O), 1660 (C=C)	448 (M+, 5.32%)	3.85 (3H, s, OCH_3), 4.4 (2H, s, NH_2), 5.6 (2H, s, NH_2), 7.4-7.7 (4H, m, Ar), 8.9 (1H, s, NH).
11	3300(NH), 3110(NH), 2210(CN), 2200 (CN) 1690 (C=O), 1678(C=C)		3.9 (s, 3H, OCH_3), 7.2-7.7(4H, m, Ar-H), 9.5-11 (2H, s, NH triazole +NH CN)
12a	3315(NH), 3200(NH), 2220(CN), 2210 (CN), 1680 (C=O), 1666(C=C)		3.9 (3H, s, OCH_3), 7.3-7.6 (4H, m, Ar-H) 8.9-8.1 (2H, s broad, 2NH).
12b	3310(NH), 3225(NH), 2210(CN), 2200 (CN) 1750 (C=O), 1690 (C=O),		3.45 (3H, s, OCH_3), 3.9(3H, s, OCH_3) 7.7-7.3 (5H, m, Ar-H), 7.9 (1H, broad s, NH)

	1678(C=C)	
13		5.6 (2H, s, NH_2,), 7.9-8.3 (4 H, broad s, $2NH_2$), 7.1-7.7 (9H, m, Ar-H)

- ^{13}CNMR of 11: 169.1, 164.3, 157.6, 151.2, 135.4, 132.0, 122.2, 121.6, 113.6, 110.1, 109.3, 103.2, 86.4, 82.1, 55.2.
- ^{13}CNMR of 12a: 161.9, 138.1, 137.0, 120.9, 113.6, 110.9, 107.1, 84.5, 79.1, 55.3, 53.6
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Biological Results:

Ten triazolopyridines were studied with respect to their analgesic and anti-inflammatory activities. Their relative potencies to Valdecoxib (Bextra®) were determined (Table 3).

Analgesic Activity:

Sixty mice of both sexes weighting from 20-25 gm were divided into 10 groups. A group was kept as control (received saline) and the second received vehicle while the third received Valdecoxib as a reference drug, whereas the other groups received the synthesized compounds.

Mice were dropped gently in a dry glass beaker of one liter capacity maintained as about 55 degrees C. Normal reaction times in seconds for all animals were determined at time intervals of 10, 20, 30, 45, 60, 90 and 120 min. This is the interval extending from the instant the mouse reaches the hot beaker till the animal licks its feet or jump out of the beaker (dose 5mg/kg). Relative potencies to Valdecoxib were determined.

From what we can see in Table 3, all tested compounds exhibited analgesic activities. The most potent are compounds **5m** and **5n** which showed higher activity than Valdecoxib. Also, the analgesic activities of the rest of the compounds approached those of Valdecoxib.

Anti-inflammatory Activity:

Carrageenan foot paw edema:

Albino male rates (100-120g) were dozed orally with the tested compounds dissolved in 20% propylene glycol in a dose of 40 mg/kg body mass one hour before carrageenan challenge. Foot paw edema was induced by injecting 0.1 ml of Carrageenan solution subcutaneously into the plantar portion of the right hind paw of each rat under light anesthesia. Initial foot paw was weighed immediately following carrageenan challenge. The swelling in each test group of animals (n = 6), 3 h after Carrageenan administration was used to calculate the percent edema remained after administration of the reference and tested compounds compared with the control group.

All the tested compounds showed anti-inflammatory activity by reducing the Edema induced by Carrageenan in the rat paw.

The activities of the tested compounds were higher than that of hydrocortisone but less than that of Indomethacin® (Standard).

Table 3. Analgesic activity of some new synthesized compounds compared with Valdecoxib):

Compound No.	10 Min.	20 Min.	30 Min.	45 Min.	60 Min.	90 Min.	120 Min.
Valdecoxib	1	1	1	1	1	1	1
5a	0.83	0.84	0.84	0.86	0.87	0.88	0.87
5d	0.69	0.66	0.85	0.85	0.88	0.88	0.89
5e	0.71	0.84	0.83	0.86	0.87	0.82	0.81
5f	0.62	0.71	0.76	0.82	0.82	0.83	0.83
5g	0.83	0.92	0.94	0.96	0.96	0.95	0.94
5h	0.61	0.61	0.73	0.74	0.76	0.76	0.76
5j	0.93	0.94	0.95	0.87	0.85	0.77	0.68
5l	0.63	0.65	0.72	0.72	0.74	0.76	0.71
5m	1.27	1.43	1.42	1.44	1.42	1.42	1.37
5n	0.96	0.99	1.39	1.48	1.56	1.59	1.43

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