Design, Synthesis and Biological Evaluation of Novel 6,7,8,9-tetrahydro-2-(2-aryloxypyrimidin-4-yl)-2*H*-[1,2,4]triazolo[4,3-*a*]azepin-3(5*H*)-ones

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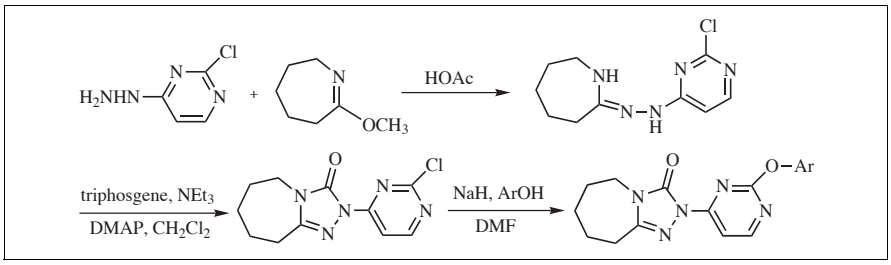

A series of novel 6,7,8,9-tetrahydro-2-(2-aryloxypyrimidin-4-yl)-2*H*-[1,2,4]triazolo[4,3-*a*]azepin-3(5*H*)-ones were designed and efficiently synthesized. Their structures were determined by IR, ^{13}C and ^{1}H NMR, mass spectroscopy, and elemental analysis. These compounds were screened for herbicidal activities against rape and barnyard grass. Compounds **5a**-**5f** and **5m** exhibited moderate herbicidal activity against rape. In addition, the synthesis of the intermediate 1-(azepan-2-ylidene)-2-(2-chloropyrimidin-4-yl)-hydrazine (**3**) was studied and the reason for the low yield in the initial procedure is discussed as well.

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Introduction.

Pyrimidine derivatives are very important molecules in biology and have many applications in the areas of pesticide [1,2] and pharmaceutical agents [3,4] such as imazosulfuron, ethirmol and mepanipyrim [5]. Recently, (4-trifluormethylpyrazolyl)pyrimidines [6,7] and 1,2,4-triazolo[1,5-*a*]pyrimidine ether compounds [8] have been found to exhibit excellent herbicidal activity against a broad range of weeds. Furthermore, a new series of highly active herbicides of substituted 2-azolyl-4-phenoxy-pyrimidines in which azole substituents were nitrogen-linked and include pyrazole, imidazole and triazole were also reported [9].

In addition, many heterocycles containing the triazolinone ring were associated with a particularly wide rang of biological properties, including 5-HT_2 antagonist activity [10], anti-inflammatory activity [11], as well as herbicidal activity [12-14]. For example, G. Theodoridis has investigated aryltriazolinone herbicides as protoporphyrinogen oxidase (Protox) inhibitors and found several highly active herbicides [15-18]. Moreover azafenidin, which was also a Protox inhibitor, has been developed and commercialized in worldwide specialty markets [19,20].

Therefore, it is attractive to develop novel pyrimidinyl-triazolinones compounds which include both the active pyrimidine and triazolinone moiety and study their potential pharmaceutical activities in order to discover highly active compounds. To the best of our knowledge, there are no reports involving the synthesis of aryloxy-pyrimidinyl triazolinones. Herein, we report our strategy for the synthesis of these 6,7,8,9-tetrahydro-2-(2-aryloxy-pyrimidin-4-yl)-2*H*-[1,2,4]triazolo[4,3-*a*]azepin-3(5*H*)-one compounds (**5**), which are illustrated in Scheme 1, and the results of their biological activities.

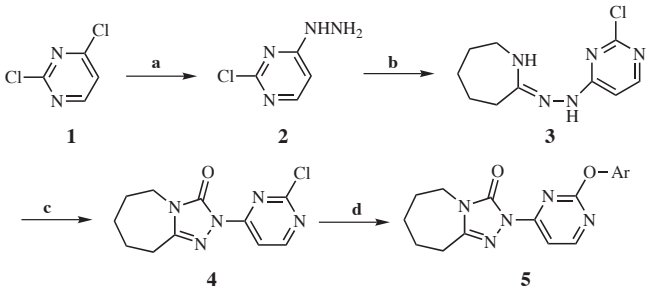
Results and Discussion.

Since the chloride at 4-position of the pyrimidine ring is more active than at 2-position, 1-(2-chloropyrimidin-4-yl) hydrazine (**2**) was obtained selectively by reaction of 2,4-dichloropyrimidine (**1**) with hydrazine hydrate in the presence of NEt_3 in alcohol.

Compound **3** was obtained in good yield (70.2%) by adding **2** into the solution of **6** in glacial acetic acid at 35 °C. Cyclization of **3** with triphosgene in the presence of NEt_3 and catalytic amount of DMAP in the solution of CH_2Cl_2 provided **4** in the yield of 44.3%. This cyclization did not proceed easily in the absence of DMAP. Since chloride eliminated easily to introduce a new bond, the target compounds (**5**) can be synthesized efficiently by the condensation of compound (**4**) with sodium aryloxides in *N,N*-dimethylformamide at room temperature.

The structures of all the title compounds (**5a-5m**) are established on the basis of elemental analysis and spectral data. Physical properties, elemental analysis, IR and MS spectra data are presented in Table 1. The

Scheme 1



Reaction conditions: **a** C_2H_5OH, NEt_3, $NH_2NH_2{\cdot}H_2O$, 0 °C to room temperature;
b glacial acetic acid, 3,4,5,6-tetrahydro-7-methoxy-2*H*-azepine (**6**), 35 °C;
c CH_2Cl_2, triphosgene, NEt_3, DMAP, 0 °C, **d** DMF, NaH, ArOH

Ar: **5a** = H-C_6H_4; **5b** = 2-$CH_3C_6H_4$; **5c** = 3-$CH_3C_6H_4$; **5d** = 4-$CH_3C_6H_4$; **5e**= 3-ClC_6H_4;
5f = 4-ClC_6H_4; **5g** = 3-$NO_2C_6H_4$; **5h** = 4-$NO_2C_6H_4$; **5i** = 3-$CF_3C_6H_4$; **5j** = 4-$MeO_2CC_6H_4$;
5k = 4-$EtO_2CCH_2O_2CC_6H_4$; **5l** = 4-$EtO_2CCH^*(CH_3)O_2CC_6H_4$; **5m** = 4-$MeO_2CC_2H_4C_6H_4$.

Table 1

Physical properties, Elemental Analysis Data, Infrared, and Mass Spectra of Compounds **5a-5m**

No.	Physical state	MF (MW)	mp. (°C)	Yield (%)	Analysis Found (Calcd.) C	H	N	Infrared spectrum ν (cm^{-1}) (KBr) / Mass spectrum (m/z (relative intensity %)).
5a	White solid	$C_{17}H_{17}N_5O_2$	184-185	58	63.33	5.39	21.39	3135, 2930, 2850, 1714 (N**C=O**), 1580, 1442 /
		323.4			63.15	5.30	21.66	323 (M^+, 37), 220 (36), 212 (21), 171 (100).
5b	White solid	$C_{18}H_{19}N_5O_2$	170-172	44	63.81	5.70	20.39	3146, 2933, 2860, 1722 (N**C=O**), 1575, 1464 /
		337.4			64.08	5.68	20.76	337 (M^+, 81), 320 (98), 226 (100), 185 (78).
5c	White solid	$C_{18}H_{19}N_5O_2$	164-166	67	64.30	5.94	20.81	3136, 2936, 2857, 1721 (N**C=O**), 1581, 1450 /
		337.4			64.08	5.68	20.76	337 (M^+, 28), 226 (15), 220 (25), 185 (100).
5d	White solid	$C_{18}H_{19}N_5O_2$	162-163	63	63.80	5.92	21.02	3131, 2925, 2857, 1723 (N**C=O**), 1576, 1458 /
		337.4			64.08	5.68	20.76	337 (M^+, 30), 226 (20), 220 (30), 185 (100).
5e	White solid	$C_{17}H_{16}ClN_5O_2$	144-145	53	56.92	4.79	19.66	3145, 2930, 2852, 1719 (N**C=O**), 1586, 1472 /
		357.79			57.07	4.51	19.57	357 (M^+, 30), 220 (40), 205 (100), 153 (11).
5f	White solid	$C_{17}H_{16}ClN_5O_2$	164-165	56	56.88	4.75	19.30	3131, 2930, 2849, 1724 (N**C=O**), 1590, 1467 /
		357.79			57.07	4.51	19.57	357 (M^+, 28), 220 (38), 205 (100), 153 (11).
5g	Yellow solid	$C_{17}H_{16}N_6O_4$	198-200	58	55.51	4.31	22.97	3104, 2937, 2857, 1724 (N**C=O**), 1593, 1525
		368.4			55.43	4.38	22.82	(NO_2), 1468, 1351 (NO_2) /
								369 (M^++1, 25), 323 (100), 221 (24), 216 (84).
5h	White solid	$C_{17}H_{16}N_6O_4$	211-213	41	55.19	4.32	23.06	3118, 2922, 2857, 1724 (N**C=O**), 1591, 1517
		368.4			55.43	4.38	22.82	(NO_2), 1467, 1350 (NO_2) /
								369 (M^++1, 17), 323 (100), 221 (30), 216 (80).
5i	White solid	$C_{18}H_{16}F_3N_5O_2$	125-126	53	55.07	4.34	17.66	3143, 2936, 2860, 1723 (N**C=O**), 1584, 1466 /
		391.4			55.24	4.12	17.90	391 (M^+, 25), 280 (16), 239 (100), 220 (25).
5j	White solid	$C_{19}H_{19}N_5O_4$	174-175	57	59.85	5.08	18.15	3149, 2947, 2851, 1724 (N**C=O**, Ar**C=O**), 1588,
		381.4			59.84	5.02	18.36	1458 /
								382 (M^++1, 100), 368 (28), 351 (15), 350 (97).
5k	White solid	$C_{22}H_{23}N_5O_6$	160-161	55	58.38	5.33	15.58	3139, 2930, 2858, 1751 (CH_2**C=O**), 1722 (N**C=O,**
		453.5			58.27	5.11	15.44	Ar**C=O**), 1577, 1458 /
								454 (M^++1, 23), 382 (100), 368 (30), 350 (92).
5l	White solid	$C_{23}H_{25}N_5O_6$	163-164	61	59.38	5.51	15.12	3134, 2932, 2860, 1751 (CH_2**C=O**), 1721 (N**C=O,**
		467.5			59.09	5.39	14.98	Ar**C=O**), 1583, 1471 /
								468 (M^++1, 32), 382 (100), 368 (29), 350 (91).
5m	White solid	$C_{21}H_{23}N_5O_4$	140-141	64	61.50	5.61	17.11	3127, 2933, 2857, 1727 (N**C=O,** CH_2**C=O**), 1581,
		409.4			61.60	5.66	17.10	1460 /
								410 (M^++1, 5), 379 (30), 378 (100), 336 (19).

difference between found value and calculated value of elemental analysis of all the compounds **5** is under 0.4%. The ^1H and ^{13}C NMR data for the compound **5** are given in Table 2.

Table 2

^{1}H and ^{13}C NMR (δ, $CDCl_3$) of Compounds **5a-5m**

5a 1.79 - 1.90 (m, 6H, $NCH_2(CH_2)_3$), 2.84 - 2.88 (m, 2H, $=CCH_2$, 3.83 - 3.86 (m, 2H, NCH_2), 7.20 - 7.45 (m, 5H, ArH), 7.95 (d, 1H, J = 5.7 Hz, pyrimidine 5-H), 8.45 (d, 1H, J = 5.7 Hz, pyrimidine 6-H) /
165.33, 160.67, 157.78, 153.03, 152.61, 152.50, 129.78, 125.62, 121.83, 103.92, 42.66, 30.78, 28.78, 28.22, 25.73

5b 1.79 - 1.90 (m, 6H, $NCH_2(CH_2)_3$), 2.20 (s, 3H, $ArCH_3$), 2.86 - 2.90 (m, 2H, $=CCH_2$), 3.83 - 3.86 (m, 2H, NCH_2), 7.01 - 7.30 (m, 4H, ArH), 7.95 (d, 1H, J = 5.7 Hz, pyrimidine 5-H), 8.42 (d, 1H, J = 5.7 Hz, pyrimidine 6-H) /
165.16, 160.77, 157.85, 152.61, 152.53, 151.53, 131.49, 130.90, 127.26, 125.95, 122.00, 103.71, 42.66, 30.77, 28.78, 28.22, 25.73, 16.60

5c 1.79 - 1.90 (m, 6H, $NCH_2(CH_2)_3$), 2.38 (s, 3H, $ArCH_3$), 2.84 - 2.89 (m, 2H, $=CCH_2$), 3.83 - 3.86 (m, 2H, NCH_2), 6.99 - 7.33 (m, 4H, ArH), 7.94 (d, 1H, J = 5.7 Hz, pyrimidine 5-H), 8.45 (d, 1H, J = 5.7 Hz, pyrimidine 6-H) /
165.45, 160.70, 157.76, 153.00, 152.59, 152.52, 139.98, 129.49, 126.51, 122.39, 118.82, 103.82, 42.66, 30.80, 28.78, 28.22, 25.75, 21.65

5d 1.72 - 1.82 (m, 6H, $NCH_2(CH_2)_3$), 2.29 (s, 3H, $ArCH_3$), 2.77 - 2.81 (m, 2H, $=CCH_2$), 3.78 - 3.79 (m, 2H, NCH_2), 7.10 (d, 2H, J = 9.0 Hz ArH), 7.22 (d, 2H, J= 9.0 Hz ArH), 7.86 (d, 1H, J = 5.7 Hz, pyrimidine 5-H), 8.37 (d, 1H, J = 5.7 Hz, pyrimidine 6-H) /
165.55, 160.66, 157.76, 152.53, 150.80, 150.60, 135.21, 130.34, 121.56, 103.78, 42.66, 30.80, 28.79, 28.22, 25.75, 21.15

5e 1.79 - 1.90 (m, 6H, $NCH_2(CH_2)_3$), 2.84 - 2.88 (m, 2H, $=CCH_2$), 3.84-3.87 (m, 2H, NCH_2), 7.11 - 7.38 (m, 4H, ArH), 7.99 (d, 1H, J = 5.7 Hz, pyrimidine 5-H), 8.46 (d, 1H, J = 5.7 Hz, pyrimidine 6-H) /
164.82, 160.63, 157.83, 153.53, 152.76, 152.45, 134.93, 130.49, 125.85, 122.44, 120.20, 104.29, 42.66, 30.75, 28.74, 28.20, 25.72

5f 1.79 - 1.90 (m, 6H, $NCH_2(CH_2)_3$), 2.84 - 2.88 (m, 2H, $=CCH_2$), 3.83 - 3.86 (m, 2H, NCH_2), 7.17 (d, 2H, J = 8.7 Hz, ArH), 7.38 (d, 2H, J = 8.7 Hz, ArH), 7.97 (d, 1H, J = 5.7 Hz, pyrimidine 5-H), 8.45 (d, 1H, J = 5.7 Hz, pyrimidine 6-H) /
164.94, 160.60, 157.81, 152.71, 152.44, 151.50, 130.83, 129.81, 123.21, 104.19, 42.65, 30.75, 28.74, 28.20, 25.72

5g 1.80 - 1.90 (m, 6H, $NCH_2(CH_2)_3$), 2.84 - 2.89 (m, 2H, $=CCH_2$), 3.84 - 3.87 (m, 2H, NCH_2), 7.58 - 7.60 (m, 2H, ArH), 8.03 (d, 1H, J = 5.7 Hz, pyrimidine 5-H), 8.11 - 8.17 (m, 2H, ArH), 8.47 (d, 1H, J = 5.7 Hz, pyrimidine 6-H) /

5h 1.79 - 1.90 (m, 6H, $NCH_2(CH_2)_3$), 2.84 - 2.88 (m, 2H, $=CCH_2$), 3.84 - 3.88 (m, 2H, NCH_2), 7.42 (d, 2H, J = 9.0 Hz, ArH), 8.04 (d, 1H, J = 5.7 Hz, pyrimidine 5-H), 8.31 (d, 2H, J = 9.0 Hz, ArH), 8.49 (d, 1H, J = 5.7 Hz, pyrimidine 6-H) /
168.78, 160.68, 157.95, 154.00, 152.97, 152.42, 144.97, 125.63, 122.19, 104.97, 42.73, 30.75, 28.76, 28.23, 25.73

5i 1.77 - 1.89 (m, 6H, $NCH_2(CH_2)_3$), 2.84 - 2.88 (m, 2H, $=CCH_2$), 3.83 - 3.86 (m, 2H, NCH_2), 7.21 - 7.43 (m, 4H, ArH), 7.95 (d, 1H, J = 5.7 Hz, pyrimidine 5-H), 8.45 (d, 1H, J = 5.7 Hz, pyrimidine 6-H) /
164.70, 160.64, 157.86, 153.14, 152.79, 152.47, 132.32, 131.99, 130.26, 125.33, 122.27 ($^{3}J_{C\text{-}F}$ = 4 Hz), 119.06 ($^{3}J_{C\text{-}F}$ = 4 Hz), 104.44, 42.68, 30.76, 28.75, 28.21, 25.72

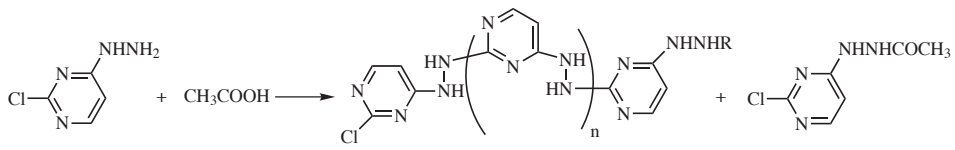
5j 1.79 - 1.90 (m, 6H, $NCH_2(CH_2)_3$), 2.84 - 2.88 (m, 2H, $=CCH_2$), 3.85 - 3.87 (m, 2H, NCH_2), 3.92 (s, 3H, $COOCH_3$), 7.30 (d, 2H, J = 9.0 Hz, ArH), 8.00 (d, 1H, J = 5.7 Hz, pyrimidine 5-H), 8.11 (d, 2H, J = 9.0 Hz, ArH), 8.47 (d, 1H, J = 5.70 Hz, pyrimidine 6-H) /
166.60, 164.63,160.65, 157.85, 156.79, 152.75, 152.44, 131.55, 127.26, 121.54, 104.45, 52.34, 42.66, 30.75, 28.75, 28.20, 25.73

5k 1.30 (t, 3H, J = 7.2 Hz, CH_2CH_3), 1.79 - 1.90 (m, 6H, $NCH_2(CH_2)_3$), 2.84 - 2.88 (m, 2H, $=CCH_2$), 3.84 - 3.87 (m, 2H, NCH_2), 4.26 (q, 2H, J = 7.2 Hz, CH_2CH_3), 4.85 (s, 2H, OCH_2), 7.32 (d, 2H, J = 9.0 Hz, ArH), 8.01 (d, 1H, J = 5.7 Hz, pyrimidine 5-H), 8.17 (d, 2H, J = 9.0 Hz, ArH), 8.47 (d, 1H, J = 5.7 Hz, pyrimidine 6-H) /
167.95, 165.45, 164.58, 160.65, 157.86, 157.20, 152.78, 152.44, 131.94, 126.32, 121.66, 104.50, 61.65, 61.44, 42.66, 30.75, 28.74, 28.20, 25.72, 14.35

5l 1.29 (t, 3H, J = 7.2 Hz, CH_2CH_3), 1.63 (d, 3H, J = 7.2 Hz, $CHCH_3$), 1.79 - 1.90 (m, 6H, $NCH_2(CH_2)_3$), 2.84 - 3.88 (m, 2H, $=CCH_2$), 3.85 - 3.87 (m, 2H, NCH_2), 4.24 (q, 2H, J = 7.2 Hz, CH_2CH_3), 5.31 (q, 1H, J = 7.2 Hz, $CHCH_3$), 7.31 (d, 2H, J = 9.0 Hz, ArH), 8.01 (d, 1H, J = 5.7 Hz, pyrimidine 5-H), 8.16 (d, 2H, J = 9.0 Hz, ArH), 8.47 (d, 1H, J = 5.7 Hz, pyrimidine 6-H) /
170.94, 165.42, 164.63, 160.65, 157.88, 157.09, 152.76, 152.45, 131.85, 126.63, 121.60, 104.48, 69.40, 61.58, 42.66, 30.75, 28.75, 28.20, 25.72, 17.30, 14.33

5m 1.79 - 1.90 (m, 6H, $NCH_2(CH_2)_3$), 2.65 (t, 2H, J = 7.5 Hz, $ArCH_2$), 2.84 - 2.88 (m, 2H, $=CCH_2$), 2.97 (t, 2H, J = 7.5 Hz, CH_2CO), 3.69 (s, 3H, OCH_3), 3.83 - 3.86 (m, 2H, NCH_2), 7.14 (d, 2H, J = 9.0 Hz, ArH), 7.25 (d, 2H, J = 9.0 Hz, ArH), 7.95 (d, 1H, J = 5.7 Hz, pyrimidine 5-H), 8.44 (d, 1H, J = 5.7 Hz, pyrimidine 6-H) /
173.48, 165.36, 160.62, 157.76, 152.61, 152.49, 151.41, 137.72, 129.63, 121.80, 103.87, 51.88, 42.65, 35.80, 30.78, 30.56, 28.77, 28.21, 25.76

Scheme 2



7 R=H, n=2, 3
8 R=$COCH_3$, n=1,2,3,...,10

Table 3
Bioassay Test of Compounds **5a-5m** Against rape and Barnyard grass (100ppm, inhibitory rate %)

	5a	**5b**	**5c**	**5d**	**5e**	**5f**	**5g**	**5h**	**5i**	**5j**	**5k**	**5l**	**5m**
rape	54.23	54.34	51.74	60.59	48.33	54.80	28.70	35.76	41.79	16.67	0.00	13.48	72.73
barnyard grass	12.00	28.37	29.70	19.32	21.40	19.72	7.34	0.00	21.07	27.16	28.06	0.00	22.71

In our initial synthesis of **3**, compound **6** was added to a solution of **2** in methanol saturated with HCl according to the literature procedure [21]. The yield was very low (<10%). When the solvent was replaced by glacial acetic acid, it was found that increasing the amount of reactants lowered the yield dramatically (40% to 10%). Variation of the reaction temperature (0-70 °C) and the reaction time (4-48 h) also failed to elevate the yield. However, compound **3** was obtained in good yield (70.2%) regardless of the amount of reactants when compound **2** was added to a solution of **6** in glacial acetic acid at 35 °C. Further investigation showed that the yield of compound **3** was largely dependent of the adding sequence of the reactants and the reaction temperature.

These results indicated that there might be some undesirable occurrence of self-polymerization of compound **2** and/or the reaction between **2** with glacial acetic acid due to the strong nucleophilic ability of the hydrazine group at the 4-position. In order to confirm this suggestion, **2** was treated in glacial acetic acid at 35-40 °C and monitored by thin layer chromatography. After 2 h, some yellow deposits (**7** and **8**) came out of the solution with little formation of **9**. After an 8 h reaction time, the mixture of **7** and **8** were collected by filtration and **9** was isolated by flash chromatography in 10% yield.

The mass spectra of mixture of **7** and **8** exhibited strong fragment ion peaks corresponding to $[M+1]^+$ of all assigned structures. The fragment ion peaks at m/z 469 and 577 showed that n was 2 and/or 3 in the compound **7**. On the other hand, there were ten fragment ion peaks every m/z 108 from m/z 403 to m/z 1375, every increased m/z 108 could be attributed to an increment of a structural unit of NH-NH-$C_4H_2N_2$. These results showed that n was in the range from 1 to 10 in the compound **8**.

Hence, the reason for the low yield in the initial procedure may be that the high concentration of unaltered **2** in glacial acetic acid induced the high probability of undesirable self-polymerization of **2** and/or the condensation of **2** with glacial acetic acid with increasing temperature. In contrast, in the improved process where **2** was slowly added into the solution of **6** in glacial acetic acid at 35 °C, the concentration of **2** was always kept at lower level and greatly decreased the occurrence of the side reaction. Furthermore, the reaction rate of **2** with **6** was slightly faster than the side reactions, so that the yield was greatly increased.

The preliminary biological activity of these 6,7,8,9-tetrahydro-2-(2-aryloxypyrimidin-4-yl)-2*H*-[1,2,4]triazolo[4,3-*a*]azepin-3(5*H*)-one compounds was evaluated against barnyard grass and rape using a previously reported procedure [22]. The biological data were presented in Table 3. The results showed that some compounds **5** possessed an inhibition effect against rape and weak against barnyard grass. For example, the inhibitory rate of compound **5d** and **5m** were 60.59%, 72.73% to rape and 19.32%, 22.71% to barnyard grass at 100 ppm respectively.

Conclusion.

In conclusion, we have reported useful methodology for the synthesis of 6,7,8,9-tetrahydro-2-(2-aryloxypyrimidin-4-yl)-2*H*-[1,2,4]triazolo[4,3-a]azepin-3(5*H*)-one compounds. An improved process to prepare intermediate 1-(azepan-2-ylidene)-2-(2-chloropyrimidin-4-yl)hydrazine (**3**) was developed, and a reason for the low yield in the initial procedure is discussed. All compounds were tested for herbicidal activity. However, only a few compounds exhibited moderate activity against rape and weak activity against barnyard grass. Further biological evaluation and structure modifications are in progress in our laboratory.

EXPERIMENTAL

General Methods.

Melting points were measured on a Thomas-Hoover apparatus and were not corrected. Infrared spectra were recorded on a Bruker Equinox55 spectrophotometer as potassium bromide tablets. ^{1}H and ^{13}C-NMR spectra were measured on a Bruker XL-300 spectrometer (^{1}H, 300 MHz and ^{13}C, 75 MHz) or Varian 400 spectrometer (^{1}H, 400 MHz and ^{13}C, 100 MHz). Mass spectra were recorded on a Thermo Finnigan LCQ Advantage LC/mass detector instrument. Elemental analyses were performed on Yanaco-CHN CORDER MT-3 elementary analyzer. The starting material, 2,4-dichloropyrimidine has been obtained from commercial suppliers.

Preparation of 1-(2-Chloropyrimidin-4-yl)hydrazine (**2**).

Hydrazine hydrate (85%, 3.50 g, 0.06 mol) was added dropwise over the course of 30 minutes at 0-5 °C, to a solution of 2,4-dichloropyrimidine (7.45 g, 0.05 mol) and NEt_3 (5.5 g, 0.055 mol) in 100 ml of ethanol. After stirring in the cold for 2 h, a heavy precipitate came out of solution. The mixture was allowed to warm and stir at room temperature for 5 h until the

reaction was completed as monitored by TLC. The suspended solid was collected and washed with water and recrystallized from ethanol to give pure white crystal in 80.1% yield; mp 175-176 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.47 (br, 2H, NH*NH*$_2$), 6.73 (br, 1H, pyrimidine 5-H), 7.97 (br, 1H, pyrimidine 6-H), 8.86 (br, 1H, *NH*NH$_2$); ^{13}C NMR (75MHz, DMSO-d_6) δ 167.62, 160.46, 157.85, 101.39; ms: m/z 145 (M^++1).

Preparation of 1-(Azepan-2-ylidene)-2-(2-chloropyrimidin-4-yl)hydrazine (**3**).

A solution of 2.82 g (0.022 mol) caprolactim methyl ether in 40 ml of glacial acetic acid at 35 °C was treated dropwise with a solution of 3.22 g (0.022 mol) 1-(2-chloropyrimidin-4-yl)hydrazine in 80 ml of glacial acetic acid over a 2 h period. The yellow solution was kept at 35-40 °C for 4 h and excess glacial acetic acid was distilled off under water-pump vacuum. The residue was treated by the dropwise addition of saturated aqueous potassium carbonate until pH = 8. The crude product was washed with water to give pure yellow solid in 70.2% yield; mp 167-169 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.79-1.89 (m, 6H, NCH$_2$(*CH$_2$*)$_3$), 2.87 (m, 2H, =C*CH$_2$*), 3.48(s, 1H, *NH*), 3.85 (m, 2H, N*CH$_2$*), 5.81(s, 1H, *NH*), 8.24 (d, 1H, J = 5.7 Hz, pyrimidine 5-H), 8.59 (d, 1H, J = 5.7 Hz, pyrimidine 6-H). ^{13}C NMR (75MHz, $CDCl_3$): δ 164.14, 160.03, 157.93, 157.63, 102.66, 44.21, 32.87, 30.63, 30.38, 25.81. ms (relative intensity %): m/z 241 (M^++2, 15), 240 (M^++1, 7), 239 (M^+, 47), 204 (100), 111 (17), 96 (15).

Anal. Calcd. for $C_{10}H_{14}ClN_5$ (239.09), C, 50.11; H, 5.89; N, 29.22. Found C, 49.98; H, 6.02; N, 29.18.

Preparation of 2-(2-Chloropyrimidin-4-yl)-6,7,8,9-tetrahydro-2*H*-[1,2,4]triazolo[4,3-*a*]azepin-3(5*H*)-one (**4**).

The hydrazine **3** (0.72 g, 3 mmol), NEt_3 (0.94 g, 9.3 mmol) and DMAP (0.04 g, 0.3 mmol) were placed in 30 ml of dry CH_2Cl_2 at –10 °C under N_2. A solution of 0.45 g (1.5 mmol) triphosgene in 6 ml of dry CH_2Cl_2 was added dropwise and the red-brown clear solution was kept at –10 °C for a further 2 hours followed by gradual warming to ambient temperature for 8 h. The mixture was quenched with 30 ml of water and partitioned between H_2O and CH_2Cl_2. The organic layer was washed with brine and dried over anhydrous sodium sulfate, filtered, and the solvent was removed *in vacuo*. The white product was isolated by flash chromatography on silica gel (200-300 mesh), eluent with petroleum ether (bp 60-90 °C): ethyl acetate (1:1, v/v, R_f=0.4) in the yield of 44.3%; mp 185-186 °C; ^{1}H NMR (300MHz, $CDCl_3$): δ 1.79-1.89 (m, 6H, NCH$_2$(*CH$_2$*)$_3$), 2.87 (m, 2H, =C*CH$_2$*), 3.84 (m, 2H, N*CH$_2$*), 8.24(d, 1H, J=5.7 Hz, pyrimidine 5-H), 8.59 (d, 1H, J=5.7 Hz, pyrimidine 6-H); ^{13}C NMR (75MHz, $CDCl_3$): δ 161.16 (CO), 160.55, 156.75, 153.16, 152.25, 107.27, 42.64, 30.58, 28.58, 28.08, 25.56; ms (relative intensity %): m/z 267 (M^++2, 33), 266 (M^++1, 19), 265 (M^+, 100), 181 (19), 168 (34), 158 (17), 156 (51).

Anal. Calcd. for $C_{11}H_{12}ClN_5O$ (265.07): C, 49.72; H, 4.55; N, 26.36. Found C, 49.58; H, 4.42; N, 26.69.

Preparation of 6,7,8,9-tetrahydro-2-(2-aryloxypyrimidin-4-yl)-2*H*-[1,2,4]triazolo[4,3-*a*]azepin-3(5*H*) one (**5a-5m**).

To a stirred suspension of 0.05 g (1.25 mmol) of 60% dispersion of sodium hydride in mineral oil in 20 ml of dry DMF at room temperature was added 0.78 mmol of (un)substituted phenols and the mixture stirred for 30 min. A sample of 0.2 g (0.75 mmol) of triazolone **4** was added, the mixture was stirred at room temperature. After the reaction was completed as monitored by TLC (petroleum ether (bp 60-90 °C): ethyl acetate (1:1, v/v, R_f (**4**) =0.4), the mixture was partitioned between CH_2Cl_2 and water. The aqueous layer was extracted with CH_2Cl_2, the combined extracts were dried over anhydrous sodium sulfate and the solvent removed. The crude product was purified by flash chromatography on silica gel (200-300 mesh), eluent with petroleum ether (bp 60-90 °C):ethyl acetate (1:1, v/v).

Treatment of 1-(2-Chloropyrimidin-4-yl)hydrazine (**2**) in Glacial Acetic acid.

1-(2-Chloropyrimidin-4-yl)hydrazine (**2**) (0.22 g, 1.53 mmol) was treated in 20 ml glacial acetic acid at 35-40 °C. After a 2 h reaction time, some unsolvable deposits came out of the solution, and the mixture was still kept stirred until the reaction was completed as monitored by TLC. The suspended solid was collected and washed with ethanol, the mixture of compounds **7** and **8** were obtained as yellow solid, mp > 250 °C; ms: m/z 403, 469, 511, 577, 619, 727, 835, 943, 1051, 1159, 1267, 1375. The filtrate was removed *in vacuo*, the white product **9** was isolated by flash chromatography on silica gel (200-300 mesh), eluent with petroleum ether (bp 60-90 °C): acetone (1:1, v/v) in 10% yield; mp 191-193 °C; ^{1}H NMR (300MHz, DMSO-d_6): δ 1.95(s, 3H, CO*CH$_3$*), 6.41(br, 1H, pyrimidine 5-H), 7.97(br, 1H, pyrimidine 6-H), 8.70(br, 1H, NH*NH*), 9.41 (s, 1H, *NH*NH); ms: m/z 186 (M^+).

Anal. Calcd. for $C_6H_7ClN_4O$ (186.03) (Compound **9**): C, 38.62; H, 3.78; N, 30.03. Found C, 38.42; H, 3.75; N, 30.33.

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