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Substituted Pyridopyrimidinones. Part 3. Synthesis of Some Novel Ether Derivatives of 4*H*-Pyrido[1,2-*a*]pyrimidin-4-one

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Abstract. A series of novel bis-heterocyclic ethers, containing 4*H*-pyrido[1,2-*a*]pyrimidin-4-one along with other five and six-membered heterocyclic rings, was obtained utilizing ethyl [(4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-2-yl)oxy]acetate (**1**), [(4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-2-yl)oxy]acetic acid (**2**) and/or [(4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-2-yl)oxy]acetohydrazide (**3**). Reaction of ester **1** with some *ortho*-hydroxy-aldehydes furnished the corresponding pyrido-pyrimidyloxypyrones. Reaction of ester **1** or acid **2** with 1,2-diamines led to some imidazoles. Also, some pyrazole, triazole, and oxadiazoline derivatives have been prepared from hydrazide **3**.
Key words: Pyrido[1,2-*a*]pyrimidinone, Ethers, Pyrazoles, Oxadiazolines, Pyrones.

Resumen. Se preparó una serie de novedosos éteres bis-heterocíclicos que contienen el anillo de 4*H*-pirido[1,2-*a*]pirimidin-4-ona, unido con anillos heterocíclicos de seis miembros, empleando [(4-oxo-4*H*-pirido[1,2-*a*]pirimidin-2-il)oxi]acetato de etilo (**1**), ácido [(4-oxo-4*H*-pirido[1,2-*a*]pirimidin-2-il)oxi]acético (**2**) o [(4-oxo-4*H*-pirido[1,2-*a*]pirimidin-2-il)oxi]acetohidrazida (**3**). La reacción del éster **1** con algunos *orto*-hidroxi-aldehidos proporcionaron las piridopirimidiloxi-pironas correspondientes. La reacción del éster **1** o el ácido **2** con 1,2-diaminas condujeron a algunos imidazoles. Asimismo, se prepararon algunos derivados de pirazol, triazol y oxiadiazolina a partir de la hidrazina **3**.
Palabras clave: Pirido[1,2-*a*]pirimidinona, éteres, pirazoles, oxadiazolinas, pirones.

Introduction

The group of pyrido[1,2-*a*]pyrimidin-4-ones is a well-known class of aza-bridgehead fused heterocyclic compounds which have miscellaneous pharmaceutical applications [1]. For example, this structural pattern is present in the known psychotropic agents risperidone and paliperidone [2,3], the human leukocyte elastase inhibitor SSR69071 [4], the antiallergic agent ramastine [5], and the antioxidants 2-arylpyrido[1,2-*a*]pyrimidin-4-ones [6] (Figure 1). As a continuation to our previous work [7], we utilized ethyl [(4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-2-yl)oxy]acetate (**1**) to obtain novel bi-heterocyclic ethers which are of expected antipsychotic activity. This expected biological activity may be due to the presence of pyridopyrimidinone and other known biologically active heterocycles such as pyrazole, imidazole, triazole, oxadiazole, pyrone, coumarin, and quinolinone in one-molecular frame [8,9].

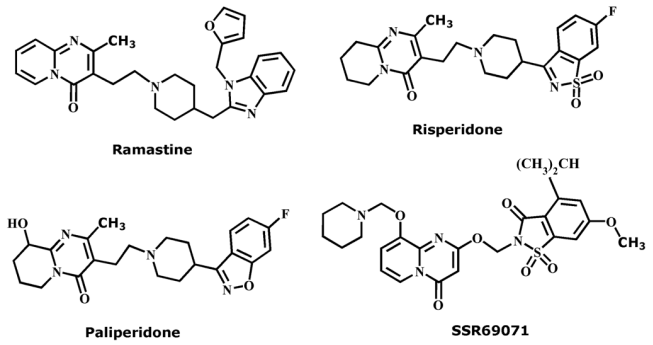
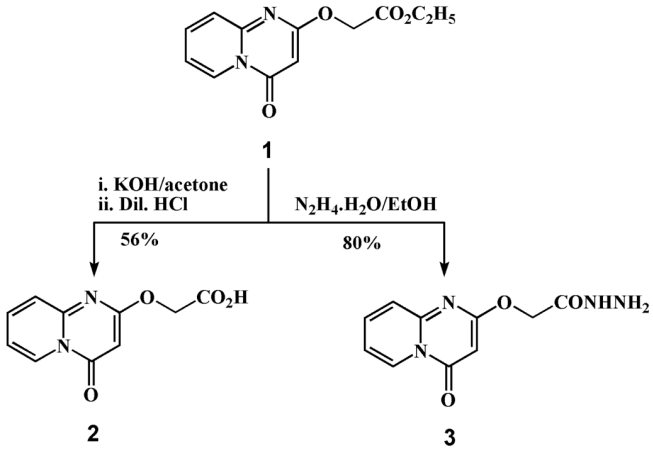


Figure 1.

Results and Discussion

The chemistry of carboxylic acids and their hydrazides is very interesting due to the capability of both carboxylic and hydrazide functions to be transformed to different azoles and azines [10]. This prompted us to convert the readily available ester **1** [7] to its corresponding free acid and acid hydrazide and thence use of both to obtain the claimed heterocycles. Saponification of the ester **1** smoothly furnished the corresponding 2-substituted acetic acid derivative **2**. The acetohydrazide **3** was obtained from the hydrazinolysis of the ester **1** (Scheme 1).



Scheme 1.

Knoevenagel reaction of α-active methylene esters with *ortho*-hydroxy-aldehydes was reported as facile synthesis of condensed α-pyranones and coumarins [11]. Thus, the reaction of the ester **1** with salicylaldehyde was performed by heating in ethanol containing piperidine as the catalyst, to give 2-[(2-oxo-2*H*-chromen-3-yl)oxy]-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**6**) (Scheme 2). IR spectrum shows evidences for this cyclization by exhibiting two absorption bands at ν 1720 and 1691 cm^{-1} corresponding to α-pyranone and γ-pyrimidinone carbonyls, respectively. In addition, ^{1}H NMR spectrum displays specific signals for α-pyridine proton at position-5 appeared as doublet at δ 8.97 while the singlet due to proton at position-3 is shown at δ 5.46. The signal of proton at position-4 of α-pyranone is observable at δ 8.43 as a singlet. Similarly the ester **1** was subjected to react with 2-hydroxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxaldehyde (**4**) [12] to afford the ether **7**. Also, reaction of the ester **1** with 4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinoline-3-carboxaldehyde (**5**) [13], under the same conditions, led to the formation of 6-methyl-3-[(4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-2-yl)oxy]-2*H*-pyrano[3,2-*c*]quinoline-2,5(6*H*)-dione (**8**) (Scheme 2). The mass fragmentation pattern of compound **7** evidences the proposed structure as illustrated herein (Chart 1).

Thermal condensation of the ester **1** with triethyl orthoformate was carried out to prepare the corresponding ethyl 3-ethoxyacrylate derivative, which is considered promising synthon for different diazoles and diazines. Indeed, this intermediate ethoxyacrylate was not separated. The elemental analysis reveals that the formula is less than the expected by C_2H_6O due to loss of an ethanol molecule during the course of reaction. However, ^{1}H NMR spectrum shows the existence of ethyl set of protons due to $CO_2CH_2CH_3$ group as triplet at δ 1.00 and quartet at δ 3.91 and the absence of (OCH_2CO) signal. Besides, there is a change in the ordinary chemical shift of the singlet due to β-pyrimidine proton which is now more downfield shifted δ 6.27. These results strongly suggest that cyclization took place and the structure of product is ethyl 4-oxo-4*H*-furo[2,3-*d*]pyrido[1,2-*a*]pyrimidine-2-carboxylate (**9**) (Scheme 2).

2-[(4/5-Methyl-4,5-dihydro-1*H*-imidazol-2-yl)methoxy]-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**10**) was prepared by thermal condensation reaction of 1,2-diaminopropane with acid **2** in about 7 % yield. This relatively low yield may be attributed to thermal decarboxylation of the acid **2** before condensation takes place. Much better yield (55%) was obtained from the reaction with ester **1**. Thermal cyclocondensation of the acid **2** with 1,2-phenylenediamine led to the formation of 2-[(1*H*-benzimidazol-2-yl)-methoxy]-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**11**) in 64 % yield. This reaction was carried out thermally in absence of solvent and interestingly, when we try to use the ester **1** under the same conditions the yield was not satisfactory. The structure of compound **11** was inferred from its IR, ^{1}H NMR spectral data and elemental microanalysis. Benzooxazole **12** and benzothiazole **13** were obtained starting from the acid **2** and 2-aminophenol or 2-aminothiophenol, under the same conditions. Recently, 1,2,4-triazoles showed potential biological activity [14]. So that it was planned to prepare a compound containing both of pyridopyrimidinone and 1,2,4-triazole in one molecular-frame. Thus, cyclocondensation of the acid **2** with thiocarbodihydrazide afforded 2-[(4-amino-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)methoxy]-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**14**). Moreover, the triazole **14** was conveniently prepared by stepwise treatment of hydrazide **3** with carbon disulfide, in presence of ethanolic potassium hydroxide, followed by *in situ* addition of hydrazine hydrate to perform cyclization of the presumed potassium dithioate intermediate (Scheme 3).

Thermal cyclization of the acetohydrazide **3** with triethyl orthoformate, in boiling DMF or in absence of solvent, smoothly afforded pyrazolinone **15**. The spectral data of the

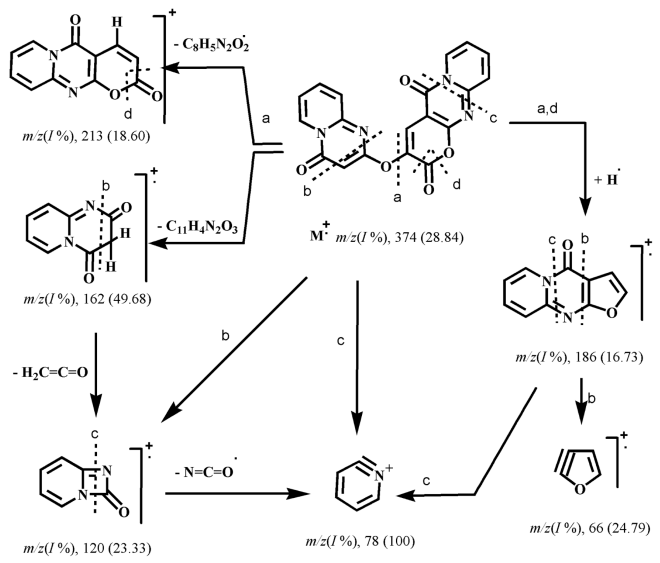
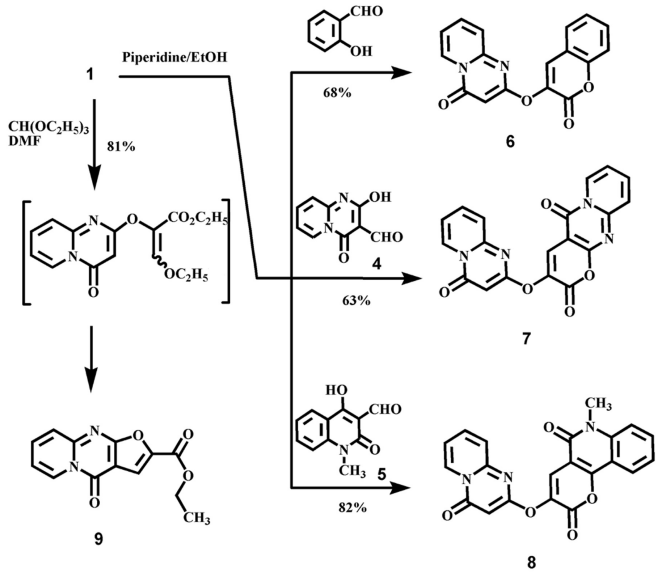
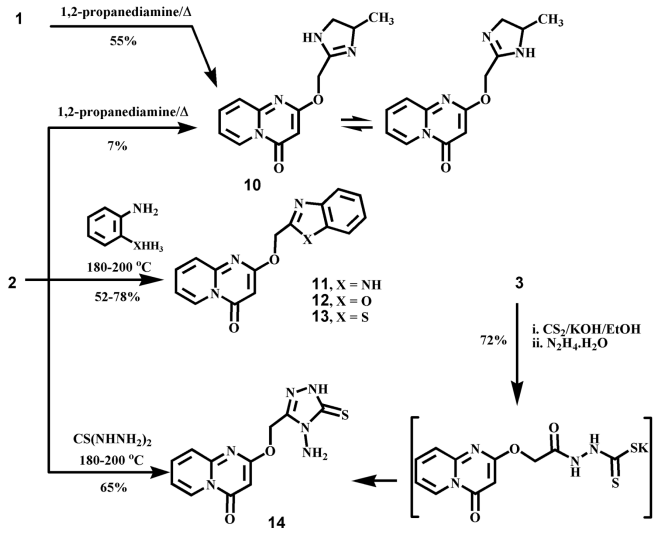


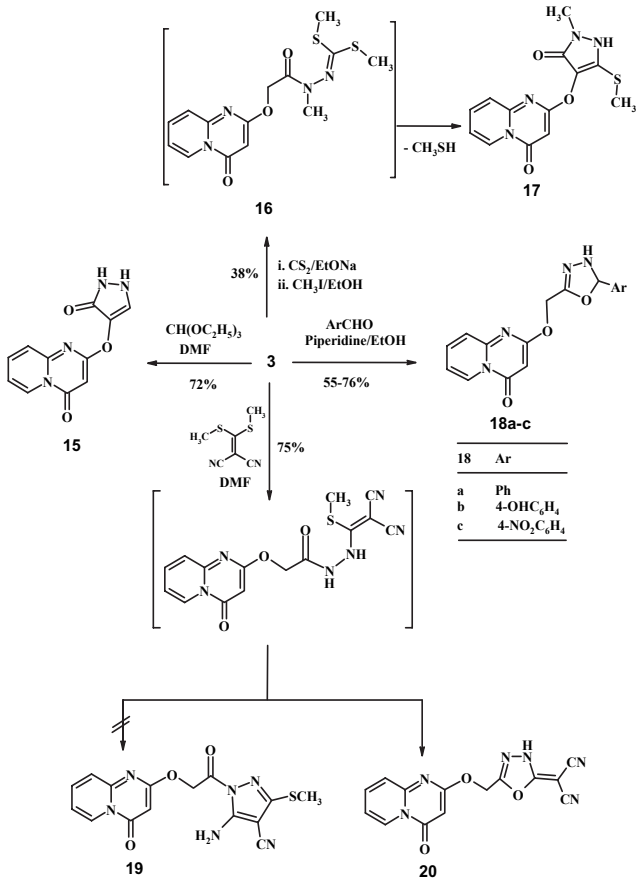
Chart 1.



Scheme 2.



Scheme 3.



Scheme 4.

product **15** revealed the disappearance of both NH_2 and OCH_2 groups, indicating their evolvement in cyclization process. 2-[(2-Methyl-5-methylthio-3-oxo-2,3-dihydro-1*H*-pyrazol-4-yl)oxy]-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**17**) was characterized as the product obtained when hydrazide **3** was treated with carbon disulfide and excess amount of methyl iodide with ^{1}H NMR spectrum of compound **17**, revealed presence of two types of methyl groups at δ 2.61 due to (SCH_3) and δ 3.41 due (NCH_3) and absence of specific signal for (OCH_2CO). The characteristic IR stretching bands at ν 1688 and 1651 cm^{-1} shows the occurrence of C=O groups due to pyrazolinone and pyridopyrimidinone systems. Formation of the compound **17** is thought to be through the expected intermediate *N*-methyl-*N'*-[di(methylthio)methylene]-2-[(4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-2-yl)oxy]acetohydrazide (**16**) which was not isolated (Scheme 4).

The reaction of hydrazide **3** with benzaldehyde, or 4-hydroxybenzaldehyde, or 4-nitrobenzaldehyde was carried out in the presence of piperidine in boiling ethanol. It is anticipated that this reaction would lead to the corresponding benzal hydrazones. Elemental microanalysis was in good accordance with this expectation. IR and ^{1}H NMR of the compound **18b** (R=OH) revealed that this hydrazone is present in a cyclic form. Thus, we observed two singlets at δ 5.02 and 5.80 due to a benzal proton and a β-pyrimidine proton, respectively along with a deuterium exchangeable proton at δ 8.13, which is attributed to an oxadiazoline (N–H) resulted from *ring–chain* tautomerism. The azomethine proton that characterizes the open chain hydrazone was merely noticed at δ 8.54 with relative integration 1:9, compared with proton at δ 5.02. IR spectrum of compound **18b** revealed additional evidence where $\nu_{C=O}$ of hydrazide that was present in start compound **3** is obviously no longer observed. Building on these observations, it was concluded that the products should be 2-[(5-aryl-4,5-dihydro-1,3,4-oxadiazol-2-yl)methoxy]-4H-pyrido[1,2-*a*]pyrimidin-4-ones **18a-c**, (Ar = C_6H_5, 4-OHC_6H_4, 4-$NO_2C_6H_4$). Even, IR spectrum of compound **18c** showed the $\nu_{C=O}$ of hydrazide at ν = 1710 cm^{-1}, but we think that derivatives **18a-c** are present in equilibrium between the two tautomers: oxadiazoline ring and hydrazone open chain (Scheme 4).

In contrary to similar cases reported by *Tominaga* [15], the hydrazide **3** when treated with [bis(methylthio)methylene]malononitrile in boiling DMF did not give the expected 5-aminopyrazole-3-carbonitrile **19**. The first surprising property of the product of this reaction is the absence of sulfur element. Secondly, no evidences for the presence of an amino (NH_2) group in both IR and ^{1}H NMR spectra. In addition, ^{1}H NMR spectrum clearly shows the loss of both methylthio groups leading to [5-{[(4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-2-yl)oxy]methyl}-1,3,4-oxadiazol-2(3*H*)-ylidene]malononitrile (**20**). The reaction seems to proceed *via* formation of the expected *N*'-[2,2-dicyano-1-(methylthio)vinyl]-2-[(4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-2-yl)oxy]acetohydrazide intermediate, which in turn underwent a thermal intramolecular nucleophilic condensation. To our knowledge, hitherto this is the first description for the use of dimethylthioketene in cyclization of acid hydrazide to oxadiazole (Scheme 4).

Conclusions

Conveniently ester **1**, carboxylic acid **2**, and hydrazide **3** derivatives of 2-(substituted oxy)-4*H*-pyrido[1,2-a]pyrimidin-4-one can be used as good synthons to obtain various diazoles, triazoles and fused pyranones of expected biological activity. The ester **1** gives much higher yield than the acid **2** when both are condensed with 1,2-propanediamine whose behavior is inversed towards 1,2-phenylenediamine. Reaction of hydrazide **3** with benzaldehydes furnished tautomeric mixture of hydrazones and predominantly oxadiazolines. Cyclization to oxadiazole with loss of two moles of methanethiol takes place instead of formation of pyrazole when hydrazide **3** is reacted with [bis(methylthio)methylene]malononitrile.

Experimental Section

General

Melting points were determined in open capillary tubes on a digital Gallen-Kamp MFB-595. IR spectra were taken on a Perkin-Elmer FT-IR 1650, using samples in KBr disks. ^{1}H NMR spectra were recorded on Varian Gemini-200 spectrometer (200 MHz), using DMSO-d_6 as the solvent and TMS as internal reference. Mass spectra were determined on a Shimadzu GC-MS-QP 1000 EX instrument by direct inlet, operating at 70 eV. Elemental microanalyses were performed on a Perkin Elmer CHN-2400 Analyzer. The preparation of ester **1** was previously described [7] and the aldehyde **5** was obtained according to literature [13]. Analytical and spectral data are listed in Tables 1 and 2, respectively.

[(4-Oxo-4H-pyrido[1,2-a]pyrimidin-2-yl)oxy]acetic Acid (2)
A solution of the ester **1** (10 mmol) in ethanol (10 mL) was treated with potassium hydroxide aqueous solution (15 mL, 2M). Then the reaction mixture was warmed at 60–70 ºC for 4h, left to cool and diluted with cold water (15 mL). The clear solution was adjusted to *p*H with 6.5 by addition of dilute hydrochloric acid. After cooling in an ice–bath for 2 h, the white precipitates that formed and was collected by filtration to give the acid **2**.

[(4-Oxo-4H-pyrido[1,2-a]pyrimidin-2-yl)oxy]acetohydrazide (3)
To a suspension of the compound **1** (10 mmol) in absolute ethanol (25 mL), was added hydrazine hydrate (20 mmol, 98 %). The mixture was stirred at 50–60 ºC for 1 h, and then the solid precipitate so formed was filtered and crystallized to afford the hydrazide **3**.

2-(2-Oxo-2H-chromen-3-yloxy)-4H-pyrido[1,2-a]pyrimidin-4-one (**6**), 3-(4-Oxo-4H-pyrido[1,2-a]pyrimidin-2-yloxy)pyrano[2,3-d]pyrido[1,2-a]pyrimidine-2,5-dione (7), and 6-Methyl-3-(4-oxo-4H-pyrido[1,2-a]pyrimidin-2-yloxy)-2H-pyrano[3,2-c]quinoline-2,5(6H)-dione (**8**)
General Procedure
Equimolar amounts (10 mmol) of the acetate ester **1** and the proper *o*-hydroxyaldehyde compound namely; salicylaldehyde or 2-hydroxy-4*H*-pyrido[1,2-*a*]-pyrimidine-3-carboxaldehyde (**4**), or 4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinoline-3-carboxaldehyde (**5**), in absolute ethanol (50 mL) containing piperidine (0.2 mL) were heated under reflux for 4–5 h. The crystalline products, which were obtained during the course of the reaction, was filtered while hot and crystallized to give the corresponding pyrones **6**, **7** and **8**.

Ethyl 4-Oxo-4H-furo[2,3-d]pyrido[1,2-a]pyrimidine-2-carboxylate (**9**)
A mixture of the ester **1** (5 mmol), triethyl orthoformate (6 mmol) and DMF (15 mL) was added and heated in a conical flask at 110–120 ºC for 30 min, then the temperature was raised to 140–150 ºC gradually over 30 min. After that the mixture was cooled to room temperature and kept in an ice-cold water bath for *ca.* 2 h. The Yellowish orange crystalline product was filtered and crystallized to give the ester **9**.

*2-[(4/5-Methyl-4,5-dihydro-1H-imidazol-2-yl)methoxy]-4H-pyrido-[1,2-a]pyrimidin-4-one (***10**)

Procedure A.
A mixture of the ester **1** (3 mmol) and 1,2-diaminopropane (3 mmol) was heated without solvent at 180–200 ºC for 30 min. Then the mixture was left to cool. The solid product that formed was crystallized to give the imidazoline **10**.

Procedure B.
A mixture of the acid **2** (3 mmol) and 1,2-diaminopropane (3 mmol) was heated without solvent at 180–200 ºC for 30 min. Then the mixture was left to cool. The solid product that formed was crystallized to give the imidazoline **10**.

2-[(1H-Benzimidazol-2-yl)methoxy]-4H-pyrido[1,2-a]pyrimidin-4-one (**11**), 2-[(Benzoxazol-2-yl)methoxy]-4H-pyrido[1,2-a]pyrimidin-4-one (12), and 2-[(Benzothiazol-2-yl)methoxy]-4H-pyrido[1,2-a]pyrimidin-4-one (**13**)

General Procedure
A mixture of the acid **2** (3 mmol) and 1,2-phenylenediamine, or 2-aminophenol, or 2-aminothiophenol (3 mmol) was heated without solvent at 180–200 ºC for 30 min. Then the mixture was left to cool. The solid product that formed was crystallized to give the benodiazoles **11-13**.

2-[(4-Amino-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)methoxy]-4H-pyrido[1,2-a]pyrimidin-4-one (**14**)

Procedure A.
A mixture of the acid **2** (5 mmol) and thiocarbodihydrazide (5 mmol) was heated in absence of solvent at fusion temperature

Table 1. Analytical Data of the New Compounds.

Compd. No	Yield %	M.p. °C	Crystaln. Solvent	M. Formula M. Weight	Microanalysis† Calcd./Found		
					C %	H %	N %
2	56	> 300	EtOH	$C_{10}H_8N_2O_4$ 220.19	54.55 54.60	3.66 3.83	12.72 12.53
3	80	220-2	EtOH	$C_{10}H_{10}N_4O_3$ 234.22	51.28 51.46	4.30 4.59	23.92 23.45
6	68	277-8	DMF	$C_{17}H_{10}N_2O_4$ 306.28	66.67 66.51	3.29 3.12	9.15 9.10
7	63	> 300	AcOH	$C_{19}H_{10}N_4O_5$ 374.32	60.97 60.70	2.69 2.63	14.97 14.62
8	82	> 300	AcOH	$C_{21}H_{13}N_3O_5$ 387.35	65.12 64.96	3.38 3.33	10.85 10.79
9	81	232-4	Acetone	$C_{13}H_{10}N_2O_4$ 258.24	60.47 60.63	3.88 4.00	10.85 10.90
10	55[a] 7[b]	188-90	EtOH	$C_{13}H_{14}N_4O_2$ 258.28	60.46 60.22	5.46 5.27	21.69 21.60
11	64	242-4	DMF	$C_{16}H_{12}N_4O_2$ 292.30	65.75 65.39	4.14 4.05	19.17 18.92
12	52	230-2	DMF	$C_{16}H_{11}N_3O_3$ 293.28	65.53 65.20	3.78 3.50	14.33 14.42
13	78	289-91	DMSO	$C_{16}H_{11}N_3SO_2$ 309.35	62.12 61.90	3.58 3.30	13.58 13.20
14	65 [a] 72 [b]	205-7	EtOH	$C_{11}H_{10}N_6SO_2$ 290.31	45.51 45.88	3.47 3.24	28.95 28.70
15	72[a] 48[b]	266-7	DMF	$C_{11}H_8N_4O_3$ 244.21	54.10 53.79	3.30 3.30	22.94 22.74
17	38	196-8	EtOH	$C_{13}H_{12}N_4SO_3$ 304.33	51.31 51.26	3.97 3.98	18.41 18.37
18a	76	230-2	MeOH	$C_{17}H_{14}N_4O_3$ 322.33	63.35 63.50	4.38 4.10	17.38 17.40
18b	58	247-50	EtOH	$C_{17}H_{14}N_4O_4$ 338.33	60.35 60.89	4.17 3.93	16.56 15.89
18c	55	267-8	EtOH	$C_{17}H_{13}N_5O_5$ 367.32	55.59 55.60	3.57 3.51	19.07 18.90
20	75	254-6	DMF	$C_{14}H_8N_6O_3$ 308.26	54.55 54.30	2.62 2.52	27.26 27.24

[a] and [b] Yields using procedures A and B, respectively.
† Sulfur analysis (**S %**) for compound **13** calcd. 10.36, Found 10.20, compound **14** calcd. 11.04, Found 10.80, and compound **17** calcd. 10.54, Found 10.40.

for 15 min. Afterwards, the obtained melt was triturated with cold methanol (10 mL) and the solidified product was filtered, washed with methanol and diethyl ether then crystallized to afford the triazole **14**.

Procedure B.
To a solution of the acetohydrazide **3** (5 mmol) in ethanol (50 mL, 95 %), fine divided potassium hydroxide (10 mmol) was added followed by drop-wise addition of carbon disulfide (5 mmol) with continuous stirring at 0–5 °C. After complete addition (*ca.* 20 min), the reaction mixture was stirred for additional 30 min at room temperature, then the obtained yellow precipitate was diluted with water till complete dissolution and hydrazine hydrate (5 mmol) was added. Then the reaction mixture was boiled until the deep greenish brown coloration persisted and left to cool in a crushed-ice bath. The fine crystals so formed were filtered and crystallized to furnish the triazole **14**.

2-[(3-Oxo-2,3-dihydro-1H-pyrazol-4-yl)oxy]-4H-pyrido[1,2-a]-pyrimidin-4-one (**15**)

Procedure A.
To a solution of the acetohydrazide **3** (5 mmol) in DMF (15 mL), triethyl orthoformate (6 mmol) was added and heated in

Table 2. IR and ^{1}H NMR Spectral Data of the New Compounds.

Compd. No.	IR (KBr), ν_{max}/cm^{-1}	^{1}H NMR (DMSO-d_6), δ/ppm
2	3508–2667 (b, OH), 1705 ($C=O_{carboxylic}$), 1650 (C=O), 1622 (C=N)	4.54 (s, 2H, OC**H$_2$**CO$_2$H), 5.66 (s, 1H, C3-H), 7.23 (t, 1H, C7-H), 7.48 (d, 1H, C9-H), 7.93 (t, 1H, C8-H), 8.90 (d, 1H, C6-H)
3	3333, 3277 (NH_2), 3250, 3197 (NH), 1687 ($C=O_{pyrimidone}$), 1651 ($C=O_{hydrazide}$), 1630 (C=N)	4.27 (b, 2H, NH_2, exchangeable with D_2O), 4.83 (s, 2H, OCH_2CO), 5.74 (s, 1H, C3-H), 7.34 (t, 1H, C7-H), 7.55 (d, 1H, C9-H), 7.97 (t, 1H, C8-H), 8.97 (d, 1H, C6-H), 9.09 (b, 1H, CONH, exchangeable with D_2O).
6	1720 ($C=O_{pyrone}$), 1691 ($C=O_{pyrimidone}$), 1632 (C=N), 1167, 1111 (COC)	5.46 (s, 1H, C3-$H_{pyrimidone}$), 7.15–7.75 (m, 6H, 4H_{arom} + C7-H + C9-H), 7.92 (t, 1H, C8-H), 8.43 (s, 1H, C4-H_{pyrone}), 8.97 (d, 1H, C6-H)
7	1714 ($C=O_{pyrone}$), 1690-1661 ($C=O_{pyrimidone}$), 1635 (C=N)	5.84 (s, 1H, C3‘-H), 7.10 (t, 2H, C7‘-H + C8-H), 7.34 (d, 2H, C9‘-H + C10-H), 7.82 (t, 2H, C8‘-H + C9-H), 8.81 (d, 2H, C6‘-H + C7-H), 9.57 (s, 1H, C4-H)
8	1722 ($C=O_{pyrone}$), 1692 ($C=O_{pyrimidone}$), 1660 ($C=O_{quinolone}$), 1632 (C=N)	3.66 (s, 3H, NCH_3), 5.21 (s, 1H, C3‘-H), 7.22–7.43 (m, 3H, 2H_{arom} + C7‘-H), 7.75–8.03 (m, 3H, 1H_{arom} + C9‘-H + C8‘-H), 8.13 (d, 1H, C10-H), 8.37 (s, 1H, C4-H), 8.94 (d, 1H, C6‘-H)
9	1757 ($C=O_{ester}$), 1669 ($C=O_{pyrimidone}$), 1633 (C=N), 1156 (C-OC)	1.00 (t, *J* = 7Hz, 3H, OCH_2C**H$_3$**), 3.91 (q, *J* = 7Hz, 2H, OC**H$_2$**CH_3), 6.27 (s, 1H, C3-H), 7.26 (t, 1H, C7-H), 7.43 (d, 1H, C9-H), 7.89 (t, 1H, C8-H), 8.87 (d, 1H, C6-H)
10	3289, 3224 (NH), 1660 (C=O), 1630 (C=N)	1.24 (d, 3H, CH_3), 3.31 (m, 1H, C4‘-H), 3.72 (d, 2H, C5‘-H), 4.47 (s, 2H, OCH_2), 5.55 (s, 1H, C3-H), 7.35 (t, 1H, C7-H), 7.54 (d, 1H, C9-H), 7.92 (t, 1H, C8-H), 8.96 (d, 1H, C6-H), 9.25-9.45 (b, 1H, NH)
11	3301, 3272 (NH), 1698 (C=O), 1640, 1632, 1610 (C=N)	4.57 (s, 2H, OCH_2), 5.63 (s, 1H, C3-H), 7.31–7.75 (m, 4H, 2H_{arom} + C7-H + C9-H), 7.85–8.08 (m, 3H, 2H_{arom}+ C8-H), 8.94 (d, 1H, C6-H), 9.68 (b, 1H, NH)
12	1690 (C=O), 1638, 1620, 1608 (C=N)	4.80 (s, 2H, OCH_2), 5.65 (s, 1H, C3-H), 7.19–7.70 (m, 6H, H_{arom} + C7-H + C9-H), 8.05 (d, 1H, C8-H), 8.90 (d, 1H, C6-H)
13	1685 (C=O), 1635, 1618, 1605 (C=N)	4.77 (s, 2H, OCH_2), 5.60 (s, 1H, C3-H), 7.12–7.72 (m, 6H, H_{arom} + C7-H + C9-H), 8.10 (d, 1H, C8-H), 8.84 (d, 1H, C6-H)
14	3440, 3268, 3182 (NH_2), 1645 (C=O), 1632 (C=N).	4.13 (s, 2H, OCH_2), 5.06 (s, 1H, C3-H), 6.93 (s, 2H, NH_2), 7.10 (t, 1H, C7-H), 7.33 (d, 1H, C9-H), 7.76 (t, 1H, C8-H), 8.82 (d, 1H, C6-H), 9.93 (s, 1H, NH).
15	3366, 3299, 3218 (NH), 1688-1645 (C=O), 1630 (C=N), 1145 (C-O-C)	5.18 (s, 1H, C3-H), 7.18 (s, 1H, C3-$H_{pyrazoline}$), 7.57 (t, 1H, C7-H), 7.85 (d, 1H, C9-H), 8.28 (t, 1H, C8-H), 8.98 (d, 1H, C6-H), 9.70 (b, 1H, NH), 10.84 (b, 1H, NHCO)
17	3250, 3199 (NH), 1688 ($C=O_{pyrimidone}$), 1651 ($C=O_{pyrazolone}$), 1635 (C=N)	2.61 (s, 3H, SCH_3), 3.41 (s, 3H, NCH_3), 5.86 (s, 1H, C3-H), 7.14 (t, 1H, C7-H), 7.37 (d, 1H, C9-H), 7.83 (t, 1H, C8-H), 8.83 (d, 1H, C6-H), 9.67 (s, 1H, NH)
18a	3172 (NH), 1692 (C=O), 1625 (C=N), 1120 (C-O-C)	4.80 (s, 2H, OCH_2), 5.59 (s, 1H, C5-$H_{oxadiazoline}$), 5.70 (s, 1H, C3-H), 7.20-7.48 (m 7H, H_{arom} ,C7-H, C9-H), 8.08 (d, 1H, 8-H), 8.50 (bs, 1H, $NH_{oxadiazoline}$), 8.90 (d, 1H, C9-H)
18b	3186 (NH), 2630 (br, OH), 1697 (C=O), 1632 (C=N), 1126 (C-O-C)	5.02 (s, 1H, C5-$H_{oxadiazoline}$), 5.49 (s, 2H, OCH_2), 5.80 (s, 1H, C3-H), 7.36 (t, 1H, C7-H), 7.56 (d, 1H, C9-H), 7.97–8.04 (m, 3H, 2H_{arom} + C8-H), 8.13 (s, 1H, $NH_{oxadiazoline}$), 8.29 (d, 2H, 2H_{arom}) 8.98 (d, 1H, C9-H), 11.89 (s, 1H, OH)
18c	3123 (NH), 1710 ($C=O_{hydrazide}$), 1677 (C=O), 1631 (C=N),	4.82 (s, 2H, OCH_2), 5.66 (s, 1H, C5-$H_{oxadiazoline}$), 5.85 (s, 1H, C3-H), 7.22-7.60 (m 4H, H_{arom}, C7-H, C9-H), 7.90-8.20 (m, 3H, H_{arom}, 8-H), 8.80 (bs, 1H, $NH_{oxadiazoline}$), 8.92 (d, 1H, C9-H)
20	3216, 3113 (NH), 2213 (C=N), 1691 (C=O), 1628 (C=N), 1146 (C-O-C)	4.93 (s, 2H, OCH_2), 5.76 (s, 1H, C3-H), 7.39 (t, 1H, C7-H), 7.56 (d, 1H, C9-H), 7.99 (t, 1H, C8-H), 8.94 (d, 1H, C6-H), 10.25 (s, 1H, $NH_{oxadiazole}$, exchangeable with D_2O)

a conical flask at 110–120 ºC for 30 min, then the temperature was raised to 140–150 ºC gradually over 30 min. After that the mixture was cooled to room temperature and kept in an ice-cold water bath for *ca.* 2 h. The Yellowish orange crystalline product was filtered and crystallized to give the compound **15**.

Procedure B.
A mixture of acetohydrazide **3** (5 mmol) and triethyl orthoformate (15 mmol) was heated under reflux for 2 h. After that the mixture was cooled to room temperature and triturated with cold methanol (10 mL). The solid so formed was filtered off and crystallized to give the compound **15**.

2-{[2-Methyl-5-(methylthio)-3-oxo-2,3-dihydro-1H-pyrazol-4-yl]oxy}-4H-pyrido[1,2-a]pyrimidin-4-one (**17**)
To a solution of the acetohydrazide **3** (5 mmol), in absolute ethanol (50mL), sodium ethoxide (15 mmol) was added, followed by drop-wise addition of carbon disulfide (5 mmol) with continuous stirring in and ice-cold water bath at 0-5 ºC. After complete addition, the mixture was stirred at room temperature for 30 min and methyl iodide (20 mmol) was dropped over a period of *ca.* 20 min, then the reactor was fitted with reflux condenser and heated at boiling for 1h. After cooling, the crystalline deposits were collected by filtration, washed with cold ethanol and crystallized to afford the pyrazole **17**.

2-[(5-Phenyl-4,5-dihydro-1,3,4-oxadiazol-2-yl)methoxy]-4H-pyrido[1,2-a]pyrimidin-4-one (**18a**), 2-[(5-(4-Hydroxyphenyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl)methoxy]-4H-pyrido[1,2-a]pyrimidin-4-one (**18b**), and 2-[(5-(4-Nitrophenyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl)methoxy]-4H-pyrido[1,2-a]pyrimidin-4-one (**18c**)

General Procedure
A mixture of the acetohydrazide **12** (3 mmol) and benzaldehyde or 4-hydroxybenzaldehyde, or 4-nitrobenzaldehyde (3 mmol), in absolute ethanol (20 mL), was treated with piperidine (0.1 mL). The clear solution was then heated under reflux for 2 h. The solid precipitate so formed during the course of the reaction was collected by filtration and crystallized to give the 1,3,4-oxadiazolines **18a-c**.

[5-{[(4-Oxo-4H-pyrido[1,2-a]pyrimidin-2-yl)oxy]methyl}-1,3,4-oxadiazol-2(3H)-ylidene]malononitrile (**20**)
A mixture of the acetohydrazide **3** (15 mmol) and [bis(methylthio)methylene]-malononitrile (6 mmol), in DMF (20 mL) was heated under reflux till evolution of methanethiol ceased (*ca.* 1h). Then, the reaction solution was left to cool at room temperature and the crystalline precipitate so formed was filtered and crystallized to give the 1,3,4-oxadiazole **20**.

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